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## SYMPOSIUM ON DISEASES OF METABOLISM

THE following clinics are included in this Symposium:

Italo F. Volini: GOUT: A REPORT OF TEN CASES FOR THE YEAR 1935

Rollin T. Woodyatt: THE PREVENTION OF DIABETIC COMA

Clifford J. Barborka: OBESITY

Robert W. Keeton: THE TREATMENT OF MALNUTRITION IN GENERAL PRACTICE

C. A. Aldrich: THE USE OF VITAMINS IN CHILDREN'S DIET

Charles A. Elliott and Walter H. Nadler: INSANITION



## CLINIC OF DR. ITALO F. VOLINI

### COOK COUNTY HOSPITAL

#### GOUT: A REPORT OF TEN CASES FOR THE YEAR 1935

Most contemporary writers when describing gout comment on its rare occurrence. Sir Thomas Clifford Allbutt in the introduction to his article on gout writes, "Although in the earlier days of my practice it was common enough, a typical podagra is now becoming less and less frequent even to rarity." However, a disease incidence of 2 per 100,000 demands more clinical attention. Arthritis clinic statistics in some instances report from 0.5 to 0.7 per cent of cases of gout. For the year 1935, in the Cook County Hospital there were 8 hospital admissions. Hench, in a series of 100 cases of gout, states that only 12 were recognized before admission in spite of the fact that plain clinical evidence was present in the majority of patients.

The following case history dramatically illustrates the serious results of such diagnostic error. M. F., male, age thirty-four, entered the hospital March 12, 1935, with a history of painful swelling and discharging wound of the left big toe. The left big toe became irritated and inflamed two months ago, following which onset alternating irregular periods of improvement and relapses were described. Four days prior to admission a physician incised the angry inflamed area which has been bleeding profusely and discharging considerable purulent material since. Examination revealed a dirty sloughing wound of the medial and upper aspect of the left toe with profuse purulent discharge. Microscopic examination revealed, in addition to the pus cells, the presence of sodium urate crystals in the discharge. The metatarsophalangeal joint was

apparently involved although the uratic crystals in the discharge were derived from adjacent tophi. Tophi were widely distributed, in both ears, in the vicinity of the many small joints of the hands and feet and both olecranon bursae. The blood uric acid was 5.75 mm. per 100 cc. The x-ray report read "The hands and feet reveal the typical bony changes of gout." The previous history dates back ten years with joint inflammation involving the feet, hands, elbows with the development of many small nodules in these locations.

He improved considerably on a purine-free diet and colchicine therapy but was released from the hospital at his own request, fourteen days after admission, with the wound still draining. No follow-up history could be obtained.

This patient attributed the most recent acute episode of his arthritis to traumatism due to excessive walking two months ago. He denied any possible influence of food or alcoholics because of careful adherence to a strict dietary regime he was educated to many years ago.

This illustrates one of the most obscure and least understood phases of gout—the pathogenesis of the acute attack. It cannot be definitely stated as has been generally maintained, that the acute crisis is the result of the sudden deposition of urates into the joints. Unfortunately, chemical analysis of local tissue and fluids in acute attacks show in many instances no deviation from the normal quantitative levels. However, it is clinically recognized that causes of excessive purine intake or of excessive purine production precipitate acute attacks of gout.

Thus the episode follows excessive food intake, especially high nucleoprotein diets, meats which elevate the exogenous purine metabolism level. The endogenous purine metabolism is elevated from the destruction of body cell nucleoprotein. Thus acute attacks are reported to follow radiation therapy, especially in leukemia; following the crisis in pneumonia from the leukocytic disintegration and absorption of the pneumonic exudate, following operations, after profuse diuresis. Naturally, these results are only found in the gouty subject.





approximately 50 per cent of the uric acid production by some method not understood. Most of the remainder is excreted in the urine. Uric acid is highly insoluble, more so in an acid medium, particularly in the presence of appreciable amounts of sodium chloride. It is to be noted here that cartilage possesses probably the highest concentration of any tissue of sodium chloride. Nucleoproteins result from the endogenous destruction of cells within the body and from exogenous sources such as meat and vegetables. Uric acid thus has an endogenous and an exogenous source respectively. In the lactating infant purines are synthesized from purine-free food by the liver most probably. This occurs also in birds, reptiles, and the spawning salmon.

We can now consider the methods by which uric acid can accumulate in the blood and tissues.

First, by an increased production due either to excessive exogenous purine intake or to excessive endogenous source production from the disintegration of cellular nucleoprotein or certain products of muscle metabolism.

Second, by insufficient elimination or excretion by the kidney.

Third, by insufficient destruction of the normally destroyed fraction of the uric acid.

Fourth, by increased synthetic uric acid built up as in the nursing infant from nonpurine sources.

Fifth, by increased affinity of tissues locally for uric acid, possibly due to hypersensitiveness with allergic precipitation. It is to be recorded that the Italian investigators have demonstrated that cartilage possesses the highest fixing power for uric acid of any tissue in the body.

The weight of evidence points to a functional disturbance of the kidney with inability to excrete uric acid. Thannhauser contends that there is always less than 50 mg. uric acid per 100 cc. of urine which is pathognomonic of gout. Case No. 3 in my series, male, age forty-one, was admitted May 25, 1935, with an afebrile polyarthritis. Blood uric acid was 7 mg. per 100 cc. Urinary uric acid on three occasions revealed 9 mg.,

18 mg., and 10 mg. per 100 cc. urine. Normally this figure should be 50 mg. per 100 cc. of urine. In the year 1935, 17 patients are reported with gout: 2 in private practice and 5 at the Cook County Hospital. None of the patients had been seen previously. They were all males, varying from thirty-five to seventy-nine years in age, average forty-nine years. The blood uric was elevated above the normal in 7 varying from 4.9 to 7 mg. Four showed tophi. Two cases showed x-ray changes typical of gout, 4 an x-ray diagnosis of arthritis.

The results of therapy of the acute attacks are usually prompt. Rest and local heat are indicated. A purine-free diet, consisting of milk, egg, fruits, bread, is necessary for three to four weeks. Drug treatment may require opiates in some form when the pain is severe. Colchicine is the remedy of choice in 1-mg. dosage three times daily reduced to twice or once a day after the second day, discontinuing it immediately if the patient has a loose stool, a toxic manifestation. This drug will lose its effect after repeated attacks. Thus, B. M., age sixty-two, Case 10 in my series, having used colchicine for eight years for numerous attacks, always with relief, obtained no result in his most recent episode. He was highly intolerable to cinchophen and neocinchophen, vomiting at the first dose. Immediate cessation of symptoms occurred when given a mixture containing codeine sulphate, potassium iodide, phenacetin and sodium salicylate.

Cinchophen and neocinchophen frequently give immediate improvement acting first as analgesics and secondly directly on the kidney to increase the uric acid output in the urine. While the beneficial action is rapid in gout it is not to be construed that arthritis which responds to cinchophen is gout. Many nongouty arthritics obtain prompt relief from pain from this drug because of its pronounced analgesic activity. Personally I believe it a more effective remedy than colchicine especially as it can be given over longer periods of time than the former alkaloid.

Intermittent and carefully supervised administration of these drugs is necessary because of the danger of resulting

toxic liver atrophy with fatal outcome. Hesitancy however in prescribing cinchophen is not warranted in the florid gouty patient when administration is accompanied by high carbohydrate intake and associated alkalis. Cinchophen is much more effective than neocinchophen and usually 5-grain doses, four to six times in twenty-four hours are adequate, using three- or four-day treatment intervals with a similar duration of no drug administration. My experience indicates quicker and more certain results with combinations of opiates, salicylates, phenacetin, iodides and cinchophen after the preliminary colchicine treatment or where colchicine fails or toxic manifestations follow its use.

Interval treatment demands the absolute interdiction of all forms of alcoholic beverages. The diet can be increased in variety but it must be stressed that overfeeding will produce attacks. Meats, fowl and fish are permitted in restricted amounts, but the rich purine-containing foods such as liver, kidneys, sweetbreads are forbidden. Recent evidence points to the provocative effects of high fat intake on gouty arthritis. A generous carbohydrate fraction with low fat percentage is to be sought for in the dietary calculation.

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## CLINIC OF DR. ROLLIN T. WOODYATT

### PRESBYTERIAN HOSPITAL

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#### THE PREVENTION OF DIABETIC COMA

PRIOR to 1921 relatively few doctors were especially interested in diabetes. The treatment called for a technical knowledge that few possessed, and except in the milder types of cases or in the earlier stages of the more severe types, it was indecisive at best, so that the average doctor had little incentive to master the subject. The discovery of insulin changed this picture.

The past fifteen years have witnessed an educational movement designed to spread throughout the profession a better knowledge of the treatment of diabetes and it has accomplished much. However, so much has been written and said that there is some danger of leaving a confused impression of the relative importance of different things, so that the doctor in more or less general practice might possibly welcome some simplification.

All the things that have been taught about the care of the diabetic patient fall into two groups, the prime essentials and the details of relatively less importance. The former are few, the latter many. I will undertake to bring out some prime essentials.

There is one thing to be known about diabetes that from the practical standpoint is more important than all the rest put together, and that is, *how to keep the diabetic patient alive*; for so long as the patient remains alive any errors in respect of the details of treatment can still be corrected and the patient can be restored to a state of health with or without some irreparable scars; but if he is allowed to die there is

nothing more to be done about that. No matter how carefully all the details may be carried out except those that are essential for the preservation of life, all the benefits of treatment are transitory.

They tell the story of a young Kentucky lawyer who was taking an oral examination for admission to the bar before a judge. The judge asked him a question on constitutional law and he knew nothing about it. Then the judge asked him a question from Blackstone and he admitted that he had never read that book. "Well!" said the judge, "just what *do* you know about the law?" The candidate said, "The statutes of the state of Kentucky, your Honor. I know all there is to know about them." "Well!" said the judge, "That is interesting and also very commendable—but, young man, do you appreciate the precariousness of your situation?" "I am not sure that I understand your Honor." "Why!" said the judge, "Do you not realize that the legislature of the state of Kentucky may now convene at any time in the next few weeks and repeal all those things—and that then you won't know a damn thing about the law?"

There are many patients in that situation. They know all the statutes of grams and calories, carbohydrate, protein, fat, etc. They keep the urine *sugar free*, report for blood sugar determination. Their weight is right and they are in excellent health, but in spite of all that they are still in a precarious situation. Some day they will go away from home and catch a cold or the "flu" or a tonsillitis or an appendicitis, or have a tooth extracted or they will be overcome by the heat or suffer a nervous or emotional strain, and then not knowing what to do they will develop acido-sis and go into coma. An intercurrent infection or whatever it is will repeal all they know about diabetes.

According to Dr. Joslin's statistics diabetic patients live on the average eleven years after the beginning of the diabetes. In many cases the diabetes itself, that is to say, the metabolic disorder that we call diabetes, is not the primary cause of death. It may have nothing to do with the patient's death or



it may be merely a contributing factor. When diabetes itself is the cause of death—and I am still referring to the metabolic disorder as in contradistinction to the underlying disease or *causa morbi*—it operates by causing acidosis which throws the patient into coma, or so lowers his resistance to the intercurrent disease that he dies of that. As a matter of fact, most young diabetics die in these ways. So acidosis alone or in combination with other diseases determines the death of many patients and has much to do with the eleven-year average tenure of life. Still the death of a patient in acid coma or as a result of an uncontrolled acidosis working in conjunction with an intercurrent disease is an accident, an accident in the literal sense of the word as applied to an automobile collision, and it is a very largely preventable accident too. No diabetic need die in coma or from the effects of an acidosis working in conjunction with other diseases. Knowledge available at the present time is sufficient for the prevention of all such deaths. Now in a series of paragraphs I will state some items of knowledge which when acquired and applied by diabetic patients have been sufficient to prevent death in acidosis.

In teaching patients what they must know in order to prevent and check acidosis, it is important to remember that they must know these things better than merely as intellectual conceptions. It is not enough that these things be explained to the patient so that he intellectually understands them. Nor is it enough that he have them inscribed on papers at home. As Foch said concerning the principles of war, "They must be ingrained as it were in the very bones so that the officer acts in accordance with them automatically, without thought." So in the case of the diabetic certain items of knowledge must be instilled to such a depth that the patient will act in accordance with them reflexly. We must establish a conditioned reflex.

The first thing to know is *when to anticipate acidosis, when to be on the lookout for it*. The next thing to know is *how to detect it in the early stages*. The third thing to know is *how to stop it*.

*When the diabetic patient has a cold he must know that that cold may or may not bring on acidosis.* The important point is the realization. If he does not realize he will not act. If he does he will be very apt to act. When the diabetic patient has a "cold" he should:

1. Examine the urine at frequent intervals. He should examine the urine *four times a day, at meal hours and bedtime.*

2. When sugar is present, he should test for *acid.*

3. When both sugar and acid are found in the urine, he should go on a suitable *Emergency Program.*

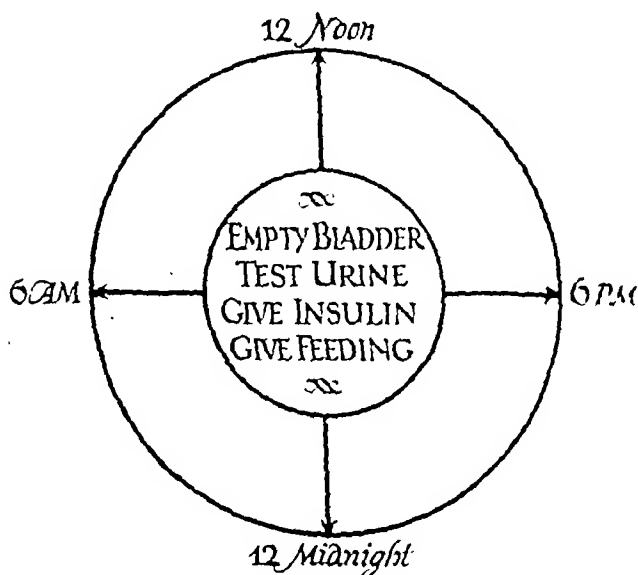
*What applies to a cold* applies in general to any intercurrent infection, any major or minor operation, a tooth extraction, a vaccination, a nervous shock, an emotional upset, and above everything else, an *omission of insulin.* A cold or anything as bad as or worse than a cold, indeed any interruption of the even tenor of the patient's health should be considered as a good reason for testing the urine four times a day, at meal hours and bedtime.

**Concerning the Ferric Chloride Test.**—The simplest way to make the test is to take 5 cc. of urine in a test tube and add 2 cc. of 10 per cent aqueous ferric chloride solution all at once. Then if the test tube is shaken there will seldom be any precipitate of the phosphate of iron to cloud the urine. The precipitate which appears when small quantities of ferric chloride solution are added to the urine can be redissolved in an excess of the reagent. *Five cc. of urine with 2 cc. of 10 per cent aqueous ferric chloride* will usually be free of precipitate and not unnecessarily diluted.

The presence of aceto-acetic acid in the urine means that the body is losing alkali. A patient who is showing aceto-acetic acid in the urine also has a greater quantity of beta-hydroxybutyric acid in the urine. These two acids entering the body from endogenous sources are being neutralized by free alkali in the body and are being excreted in the form of salts, thus carrying away a part of the base that formerly existed in the form of free alkali in the body. *The alkali*

reserve is being depleted. Continued depletion will lead to coma. Aceto-acetic acid in the urine means alkali bleeding. Know when to be on the lookout for it. Look for it. Find it, and immediately stop it. How shall we do this?

(A) In the early stages, before the ketosis has resulted in enough depletion of the alkali reserve to cause clinical symptoms (symptoms of acid intoxication), the following procedure has proved effective in practice with hundreds of



The diagram shows a circle representing a twenty-four-hour day divided into four quarters of six hours each. At the beginning of each period the patient does the four things in the inner circle. The diagram assists in his education.

patients during a period of fifteen years. Other procedures may be as good. I know the soundness of this.

**Emergency Program.**—Divide the twenty-four hours into four periods of six hours each. At the beginning of each period

1. Empty the bladder.
2. Test the urine for sugar and acid.
3. Give a dose of insulin.
4. Give a standard feeding.

A *standard feeding* consists of 400 cc. (2 glasses) of milk or 300 cc. of orange juice.

*The first insulin dose:* One quarter of the patient's regular dose for twenty-four hours plus 5 units.

*The second dose:* Five units more than the first if acid is still present.

*Following doses:* Increase the dose by 5 units each period until acid is absent.

*Later:* Adjust the dose from period to period as requisite to control the glycosuria and insulin reactions.

*Note:* In the event that the patient is on protamine insulin, leave the protamine insulin dosage alone, that is to say as it has been before, and superimpose the emergency program on it.

**(B) With Early Symptoms of Acid Intoxication.**—The program may be the same as (A) (for ketosis without any toxic symptoms) with the following exceptions:

1. When there are symptoms of beginning intoxication *omit the feedings until the symptoms are gone.*

2. Make the *first dose of insulin decisive*, so that the symptoms will disappear within the first six hours. With early symptoms a decisive dose may be  $\frac{1}{2}$  to 1 unit per kilo of body weight. *Do not be afraid of insulin reactions in the presence of symptoms. Be afraid of coma.*

When the symptoms are stopped, insulin reactions can easily be prevented by hourly feedings of 50 to 100 grams of orange juice, or more if required. The hourly feedings should be enough to maintain some glycosuria. So long as sugar is passing through the kidneys into the urine there is no danger of insulin reaction. Patients sometimes gain the impression that insulin reactions and glycosuria may occur together. This is not true. The patient may pass sugar-containing urine into the bladder in one hour and sugar-free urine the following hour. In the second hour he may have an insulin reaction. Urine voided at this time may contain sugar, but this sugar was secreted the hour before and has lain in the bladder. Unless the bladder has been emptied sugar secreted

prior to the occurrence of the insulin reaction may still be present at the time when the insulin reaction occurs.

As soon as the symptoms of acid intoxication have been considered, the case becomes one of ketosis without any clinical symptoms and treatment proceeds as under (A).

If all patients and doctors were on the lookout for acidosis and if they discovered it in the early stages and would carry out some such simple procedure, acidosis would seldom progress to the point of producing any clinical symptoms at all. However, too often it goes undiscovered and symptoms appear. Even then as a rule there is plenty of time to stop the affair without serious trouble if the early symptoms are recognized. Therefore, in the education of a patient it is important to inculcate a definite knowledge of

*The early symptoms of Acid Intoxication:*

1. *Weakness* where none has existed before, or accentuation of a previously existing weakness.
2. *Anorexia or nausea or nausea and vomiting.*
3. *Inclination to rest or sleep by day.*
4. *Increased rate of respiration* that may be present at rest or only after a mild exertion.
5. *Retardation of the mental reactions.*
6. *Facial flush.*
7. *Acetone odor on the breath.*

*If a diabetic patient has any one or more of these seven symptoms he should examine the urine for sugar and acid. Unusual fatigue or anorexia or nausea in a diabetic should be considered as evidence of acidosis until tests have shown that none exists.*

With the development of more severe symptoms of acid intoxication, the condition of the patient is usually such that he is incapable of doing anything about it. We have been discussing especially the *prevention* of coma. With more than mild or early symptoms the time for prevention has already passed and we must speak of the treatment of the precomatose patient. However, the management may still be conducted by six hourly periods. I will not undertake to discuss

in detail all phases of the treatment of the precomatose case, but I will undertake to state some steps that may well be taken in the first six hours.

(C) **First Period Management of the Precomatose Case.**—In the first period the following steps may be taken:

1. *Give a maximum dose of insulin.*

Establish at once as much insulin action as can be produced by any dose. In critical cases repeat the original maximum dose in the middle of the period, three hours after the original dose. Two units per kilo of body weight will probably produce as much effect as a larger dose. Having giving the initial maximum dose, give

2. *A cleansing enema*, to be followed by

3. *A retention enema* of normal salt solution which may have a volume of 6 cc. per kilo of body weight. In these cases the bowel is an invaluable vehicle for the administration of water. Do not dilate it by undertaking to give too much fluid by bowel at any one time, and do not irritate it by introducing sugar, bicarbonate, or any other foreign substance. Experience has shown that 6 cc. of warm normal salt solution per kilo of body weight will usually be retained when given by bowel each six hours for a number of periods. Attempts to give more very often result in the retention of less in twenty-four hours.

4. *Aspirate the stomach contents* in order to remove any acid that may have accumulated and to detect dilatation or atony of the stomach if this be present.

5. Conditions permitting, *give water by mouth* at the rate of 100 cc. per hour per 70 kilos of body weight ( $1\frac{1}{2}$  cc. per kilo of body weight). If there is any doubt as to the ability of the stomach to move this quantity of water through the pylorus, aspirate again in three or four hours to be sure that the water is passing through. If it is not moving through do not continue for fear of dilating an atonic organ. Let the stomach rest for a while and try again later.

If 3 and 5 are successfully carried out, the total water administered for the six-hour period will amount to 1000 cc.

in the case of a patient weighing 70 kilos (14 to 15 cc. per kilo). This rate of water supply continued for two or three periods will usually suffice to overcome symptoms of dehydration. If this can be done by the alimentary route, there is no need for parenteral administration.

With an incompetent stomach, colon or both, the same quantity of water may be given per period, but in this case it will be necessary to administer the water by a parenteral route. For this purpose normal salt solution by the continuous subcutaneous drip is very effective. If 1000 cc. of water are to be given in the six-hour period by the parenteral route alone, the average rate of administration is 170 cc. per hour. If the bowel will carry 400 cc. and the stomach none, 600 cc. will remain to be given by the parenteral route and so on. There is rarely if ever any need for intravenous injection of any kind. I very seldom go into the vein for any purpose in the treatment of the acidotic case.

In the first six hours of the treatment of a deeply toxic case, it is virtually impossible to overcome the acidosis and hyperglycemia to such an extent that there need be any thought of an insulin reaction or the necessity of administering any sugar. In subsequent periods the need may arise but not in the first. When it does arise, as shown by a failing glycosuria, enough sugar should be given every hour to keep some passing into the urine. By that time it can often be given by mouth. In any event it can always be given by the subcutaneous drip in the form of 10 per cent glucose solution, until the patient is entirely out of danger. Do not let the fear of an insulin reaction cause an unwise cut of the usual dosage. Keep up a plentiful insulin dosage and maintain a moderate glycosuria by hourly sugar administrations. Five to 10 Gm. an hour will usually do, even with excessive insulin dosage. If it can be given by mouth, as 50 to 100 Gm. of orange juice per hour or any equivalent, so much the simpler. If not, it can always be given as 10 per cent glucose under the skin at the rate of 50 to 100 cc. per hour.

The value of the knowledge discussed above can be illustrated by citing the following case.

A man, twenty-eight years old, had been a diabetic since the age of twenty-four. For three years he had been living on a measured diet and insulin. In these years he had remained in excellent condition under the care of a skilful doctor. This patient was well trained in all matters pertaining to quantitative dietetics, administration of insulin, examination of his urine for sugar, etc. He reported to his doctor at frequent intervals for blood sugar examinations and kept a careful diary of his condition. He had no serious difficulties until on a certain occasion he came to Chicago on a business trip.

The weather at this time was exceedingly hot. He was involved in a nervous and emotional strain. On Saturday evening he felt excessively tired. On awakening Sunday morning he was weak and nauseated. Because of the nausea he ate no breakfast and because he ate no breakfast he was afraid to take insulin for fear he might have an insulin reaction, so he omitted his usual morning dose. All day Sunday he felt weak and nauseated. He ate no food and took no insulin.

I saw him in his hotel on Monday morning. He was lying in bed flushed, dry, excessively thirsty, breathing deeply and with difficulty, in typical air hunger. He was given at once a maximum dose of insulin and taken to the hospital, and eventually recovered but only as a result of strenuous treatment.

This patient had not been taught that such a thing as a nervous or mental strain especially with the weather as hot as it was, might be calculated to bring on acidosis. He had the equivalent of a cold but did not "realize" what a cold might do. He had no ferric chloride solution. In fact, he had not been taught to make a ferric chloride test. He had not been taught the early symptoms of acid intoxication. He did not know that the excessive fatigue that he felt Saturday night was highly suggestive. He did not know that in a diabetic patient the occurrence of nausea should be regarded as



evidence of acid intoxication until it has been proved to be due to something else. He did not know that under any conditions and especially under the conditions that existed Sunday morning an omission of a dose of insulin would probably throw him into coma. In other words, this patient had been thoroughly trained in many of the technical aspects of treatment but he had not been trained in the prime essentials, and he came perilously close to death in coma.



## CLINIC OF DR. CLIFFORD J. BARBOCKA

DEPARTMENT OF MEDICINE, NORTHWESTERN UNIVERSITY  
MEDICAL SCHOOL AND PASSAVANT MEMORIAL HOSPITAL

### OBESITY

DISORDERS of metabolism frequently are encountered in medical practice. One of the commonest disorders of metabolism is obesity. Failure on the part of physicians to understand the proper management of obesity or to be sympathetic and interested in directing reducing measures for the patient seeking their counsel, results all too frequently in the overweight seeking relief by quack remedies which in all too many instances lead to definite harm to body tissue and the patient's health.

All too often the intelligent patient receives the reaction of ridicule and is impressed with the idea to leave well enough alone when he seeks medical advice. I feel confident that the reason for the various quack advice and remedies for obesity with all the ridiculous measures and diets that are undoubtedly unsound and harmful can be traced to the failure of the medical profession to give the subject its proper consideration. The laity should be taught that one of the important phases of preventive medicine is the fact that to be overweight beyond a certain limit may be the sign of some serious metabolic disturbance and relief will be sought early.

With the changes in the mode of living that characterize present-day urban existence, a considerable proportion of the adult population indulges in comparatively little muscular activity. Eating habits developed during adolescence, when the demands of physical activity necessitate a large food intake may be continued after the need for a high energy intake has

ceased. It is hard for most people to believe how a small quantity of food can influence weight. An intake of 100 calories a day above the energy expenditure means an increase in weight of about 10 pounds in a year. Reducing by increased exercise is not an easy matter, frequently is ineffective, and in some cases may even be injurious. Those who wish to get rid of accumulated body fat must eat fewer calories than they expend in activity.

### DIAGNOSIS OF OBESITY

The diagnosis of obesity usually presents very little difficulty. The physical appearance of the individual is sufficient ordinarily to make the diagnosis simple, even for the layman. Obesity does not develop rapidly in the average individual and is usually well advanced before the patient seeks medical advice.

One must, of course, differentiate:

**Myxedema**, although usually the patient has associated symptoms of hypothyroidism such as a dry skin, dry and brittle hair, mental retardation, typical facial appearance, intolerance to cold and, of course, the laboratory evidence characteristic of the disease.

**Edema**.—Occasionally widespread involvement of anasarca or ascites may superficially resemble obesity; however, careful physical examination will usually render the diagnosis a simple one.

**Avitaminosis**.—In times of financial depression, such as we have recently had, and in certain long-standing cases of poor food habits, foolish and inadequate diets to reduce an obesity there is apt to be a vitamin and mineral deficiency and these patients may develop a certain amount of subcutaneous edema and a puffy appearance of their skin simulating obesity. A careful food history and the rapid disappearance of the apparent obesity occurs on a diet that is adequate in vitamins and calories.

With these few facts differentiated and eliminated it is important, both from the standpoint of completeness of diag-

nosis and as a guide to correct therapy, to make an effort to classify the patient as to his type of obesity.

### DISCUSSION OF OBESITY

The apparent paradox that certain persons get fat and others do not on what appears to be equivalent diets invites much speculation. The old classification of exogenous obesity attributed to inactivity and overfeeding, and endogenous obesity, or the constitutional type, for which a variety of physiologic and pathologic functions has been ascribed, is subject to attack on the basis of Newburgh's contention of obesity, namely, that the subject takes in more than is used up regardless of any disease or any inherited tendency which may be present.

There can be no doubt that obesity is often the result of overindulgence in food and lack of exercise. There are persons, however, who gain weight on what appears to be a moderate intake of food, or even a restricted intake, and who indulge in considerable exercise. In many instances there seems to be an hereditary background as though there was a constitutional tendency to obesity. Many common factors may be observed in the accumulation of evidence of the incidence of the development of obesity. In many cases obesity develops following lactation because of the fact that the young mother in her zeal to supply adequate nourishment for her baby overeats and pushes fluids to a maximum. It is common for obesity to follow convalescence from an operation or from prolonged illness. There are natural periods of alterations of flesh which tend to occur at certain physiologic epochs, as puberty, menses, pregnancy, and menopause.

The problem of obesity in its many aspects has been receiving more attention in recent years and is becoming a significant factor in clinical practice. One of the chief reasons that bring most obese women to the physician is the lack of grace and beauty of figure which, in turn, is likely to bring about certain psychic effects. As a matter of fact, the final impetus that brings the obese person to the physician is one of the sequelae

of obesity rather than the esthetic considerations. Certainly it is the adverse effect on longevity and the predisposition to secondary pathologic changes that should concern the physician. The medical actuarial tables on mortality statistics quickly point out the effects of obesity on the duration of life. The per cent ratio of actual to expectant death of overweight men and women increases proportionally to each 10 pounds of overweight. This fact is recognized by insurance companies, who regard obesity as a serious impairment, and the obese person who desires life insurance has his rate increased considerably because of the extra risk associated. Not alone does the obese individual have a physical and economic handicap, but the abnormal adiposity predisposes to other pathologic conditions. Joslin has emphasized the relation of obesity to diabetes. He found that 70 to 85 per cent of persons with diabetes gave a history of obesity. If there is a latent tendency to diabetes the development of obesity certainly seems to precipitate glycosuria. It is surprising how often the history of obesity is present at the onset of glycosuria. Furthermore, the carbohydrate metabolism seems to be altered, as 40 to 60 per cent of all obese persons have an abnormal glucose tolerance. Foster stated that 50 per cent of patients with hypertension are obese. A large proportion of patients with cholelithiasis are overweight. The development of cardiac embarrassment is likewise a common observation. There also are many minor difficulties, such as varicosities, excessive perspiration and eczema, that arise from obesity. The surgeon is well aware of the poor surgical risk and the possibility of postoperative hernia and the tendency to pneumonia. Many orthopedic problems are aggravated or precipitated by overweight. It has long been known that a certain relation exists between obesity and complete or partial sterility. Some authorities feel that obesity is an exciting cause of sterility although other facts suggest that sterility is primary and that obesity supervenes as a result of metabolic disturbances produced by the elimination of the reproductive functions.

From this brief review it is apparent that obesity, regard-

less of the mechanism by which it may be produced. From a simple gain of 10 to 20 per cent above the normal weight for a certain height, sex, and age, up to veritable monstrosity, should be considered pathologic.

Various endocrine dysfunctions are accompanied often by different types of adiposity and certain regional distributions and peculiar configurations.

Many enthusiasts have suggested that all cases of obesity are due to some fault of the endocrine system. The foreign investigators particularly have emphasized this etiological factor. It requires considerable study and observation to classify definitely any case of obesity and the tendency to attribute all adiposity to endocrinopathy must continually be guarded against.

There can be no question that there are certain cases of obesity which have been definitely linked with endocrinopathies such as pituitary syndromes of adiposis dolorosa, Fröhlich's syndrome, pituitary basophilism, the generalized adiposity of certain cases of hypothyroidism, the eunuchoid type of obesity, and the obesity of hyperadrenalism.

Many other cases of obesity may be of endocrine origin, but there is no justification in classifying them as such unless there is some definite proof of faulty function of some of the glands of internal secretion available. In other words the tendency should be to suspect each case of obesity as not due to faults of glands of internal secretion until you have ruled out the more common causes of adiposity.

The endocrinopathies which have been associated with obesity are:

**Thyroid hypofunction** may possibly cause increased storage of fat by decreasing the basal metabolic rate and thus allow insufficient output of energy to balance the increase in calories. On the other hand, one should not forget that many cases of hypothyroidism are below the average weight. As a matter of fact, in observing the studies of the basal metabolism associated with obesity it is surprising to note how few cases actually have hypothyroidism.

Evans and Strang were the first to emphasize the importance of the correct method of calculating the basal metabolic rate in obese patients; stating that the weight used should be the ideal or expected weight rather than the actual weight. As a matter of fact, in order to justify the diagnosis of hypothyroidism in the presence of obesity the basal metabolic rate must be below normal when the calculation is made according to the ideal weight, rather than the actual weight of the patient, or the patient must present definite clinical symptoms of myxedema.

**Pituitary dysfunction** has been thought for many years to be the cause of certain types of obesity such as dystrophia adiposogenitalis, adiposis dolorosa (Dercum's disease), the adiposity of pituitary basophilism (Cushing's disease) and others. The work of certain investigators suggests that these conditions might not be due so much to the disturbance of the pituitary itself but possibly to the irritation of the underlying brain structure. Evans' work, in which hypophysectomies without injury to the underlying brain tissue is regularly followed by perfect dwarfism without any trace of adiposity, is exceedingly interesting.

The work of Anselmino and Hoffman indicates that there may be a hormone elaborated by the anterior lobe of the pituitary that has something to do with fat metabolism.

**Adrenals.**—It is thought by some investigators that a hormone from the adrenal cortex fixes the blood fats of the tissues. If the adrenal produces obesity, it does it by just the opposite mechanism to that of the thyroid. In other words, hypofunction of the adrenals causes weakness and decreased nutrition; while in hyperadrenalism there is every evidence of exaggerated metabolism. Koster and his associates recently have removed the suprarenal glands with relief of the obesity.

**Gonads.**—Hypofunction of the ovaries has been recognized for many years as one of the most important endocrine causes of obesity. The majority of cases of ovarian failure show an increased tendency to gain weight. This is particularly true of cases of obesity occurring before the menopause. The fre-



quent tendency for obesity to develop in patients where there is ovarian unrest such as puberty, postnuptial sterility, lactation, and the menopause seem to indicate that the ovaries play an important role. Castration or testicular failure in the male causes a definite excess of adiposity.

Two or three other facts should be mentioned in discussing the question of obesity:

**Central Nervous Lesion.**—Weir Mitchell in 1880 suggested what he called a "fat center," which is located in the posterior part of the medulla. This so-called "theory" or "central theory" has been revived by Bernhardt in Germany and Wilder in this country. Wilder suggests that the center is one of the visceral nuclei of the tuber cinereum and the walls of the fourth ventricle. The mechanism as to how this is accomplished is of course problematical, although Wilder feels it is indirectly through the control of the appetite.

**Defective water and salt metabolism** leads to overweight but this is not a true obesity.

### TREATMENT OF OBESITY

In actual practice it is quite difficult to know where exogenous obesity ends and endogenous begins, and in treating the two types of cases very little difference is found in their reaction to the dietary regimes.

The important factors in the dietary treatment of overweight and obesity are:

1. Low calorie content.
2. Adequate protein.
3. Moderately low carbohydrate content.
4. Very low fat content.
5. Sufficient bulk to satisfy hunger.

The important factors in the dietary treatment outlined above need some further discussion.

**Low Calorie Content.**—The caloric intake of the individual at hand is the first thing to be considered and, of course, it must be below the energy requirement of the patient. The calories should be high enough to meet the basic needs of

the body and teach good food habits. One should choose a caloric intake of from 800 to 1,400 calories per day, dependent upon the amount of overweight, the rate at which one desires to reduce, the expected or ideal weight desired, and whether there are any associated problems or complications. Too low a caloric intake is not a good procedure to follow routinely as it does not allow for good food habits and adequate intake of vitamins and minerals. It has poor satiety value and may cause too rapid a reduction of weight with too rapid changes in the tone of the tissues.

**Adequate Protein.**—The protein intake must be adequate to maintain nitrogen equilibrium. This may be covered by using 1 Gm. of protein per kilogram of expected or ideal weight. In addition to the protection of nitrogen balance one should choose proteins of high biologic values, so as to insure the necessary amount of all the amino-acids that aid in the building of the body's tissues. Such proteins are meat, eggs, milk and cheese.

**Moderately Low Carbohydrate Content.**—The carbohydrate content of the reduction diet must be quite limited if much weight is to be lost, yet high enough to maintain nitrogen equilibrium. Strang, McClugage and Evans report that 0.6 Gm. of carbohydrate for every gram of protein used is necessary in a reducing regimen to maintain nitrogen balance. Carbohydrate acts as a protein sparer by protecting the anti-ketogenic fraction of the protein molecule from being transformed into available glucose. In our plan of a reduction diet we use 0.85 Gm. of carbohydrate for each gram of protein used in the diet. This amount is safely above the minimum requirement to preserve nitrogen balance and insures an acid-base equilibrium, avoiding the dehydration effects of acidosis or the hydrophilic tendency of the tissues with alkalosis.

**Very Low Fat Content.**—Fat is the one foodstuff that must of necessity be very low in amount because of the number of calories allowed in a reduction diet and the high caloric value of the fat as compared to the carbohydrate and protein. The purpose of the diet is to give very little fat by mouth in

order that the body may use up its own fatty tissues to make up the deficient caloric intake of energy requirements.

**Sufficient Bulk to Satisfy Hunger.**—The satiety value of the diet is very important. The diet should be planned so that the individual should not be hungry and at the same time should be able to carry on his normal activity. Liberal quantities of green vegetables are given so as to supply sufficient bulk and roughage to aid in bowel elimination and to satisfy hunger. Meat is one of the foods that has a particularly high satiety value. The use of a small amount of fruits at the end of a meal aids a great deal in giving a sense of fulness and satisfaction. Clear meat broths (without fat) are also an aid and have no food value.

By following such a program one will insure a normal metabolizing mixture regardless of the calories given by mouth. In addition, the patients will not ordinarily experience any clinical discomfort, after the first few days, and will tend to lose weight uniformly. It is best to reduce weight gradually by prolonging the period of dieting. This is of advantage in that it accustoms the patient to a small amount of food, so that he is not likely to overeat after the weight has been sufficiently reduced. Also slow reduction lessens the chances of weakening the patient.

#### DIRECTIONS FOR APPLICATION OF DIETS

For reduction of overweight of only a few pounds one can ordinarily attain the desired weight by restricting the obvious fats and the more concentrated carbohydrates of the diet. This may be done by following the typical foods allowed and curtailing those to avoid.

## SIMPLE QUALITATIVE RESTRICTION

Typical foods allowed in reduction diets:

Milk, skimmed and buttermilk.

Egg.

Meat, lean.

Meats low in fat, as:

Chicken—lean portion.

Liver.

Fish, other than salmon.

Shrimp.

Crab meat.

Fruit, 5 and 10 per cent.

Vegetables, 3 and 6 per cent.

Clear soup.

Typical foods to avoid in reduction diets:

Sugar and all sweets.

*Starches as:*

Bread.

Cereals.

Macaroni.

Spaghetti.

Pastry, pie, cakes.

Sweet desserts.

Vegetables high in carbohydrates as:

Potato.

Shelled peas.

Shelled beans.

Corn.

Parsnips.

*Fats as:*

Butter.

Salad oils.

Cream.

Meats high in fat as

Pork.

Lamb chop with large amounts of fat

For the cases of obesity needing greater dietary restriction we have presented three series of reduction diets, calculated by

applying the important factors outlined above, on the basis of an expected or ideal weight of 160 pounds, with varying caloric values from 800 to 1200 calories per day. Diets as low as 800 calories are arranged with adequate vitamins, minerals and salts.

The ideal weight of an individual is determined usually by consulting tables of actuarial standards, choosing the weight on the basis of height, age and sex. It must be remembered that most of the tables of actuarial standards for ideal weight and height are prepared for insurance companies. These tables should serve as an approximate guide and should not be followed exactly. One must take into consideration each individual and use as a goal the best expected or ideal weight for his particular needs, both mental and physical.

Regardless of what the ideal weight should be, the first reduction diet chosen should seldom be more than 20 to 40 pounds below the present weight of the individual, depending on the type and degree of obesity and the patient's tolerance of the loss of weight. For example, a patient weighing approximately 200 pounds should use one of the diets outlined on the basis of an expected weight of 160 pounds.

When a reduction of 10 to 40 pounds has been obtained it is well to add enough food to any diet used so as to maintain the new weight for a period of two to four months. This will allow the body to readjust its metabolism for this newly attained weight prior to further reduction if necessary. The only exceptions to this rule are the cases in which obesity for certain definite reasons requires very rapid reduction, or cases of extreme obesity in which the individual weighs from 280 to 350 pounds.

During this reduction regime one should weigh only once a week, but on the same scales, at the same time of day and before the meal. The approximate average mineral content of the reduction diets outlined are:

<i>Calcium</i>	<i>Phosphorus</i>	<i>Iron</i>
0.783	1.188	0.0134

# REDUCTION DIET FOR EXPECTED OR IDEAL WEIGHT OF 160 POUNDS

(800 Calories)

## QUANTITATIVE AND ESTIMATED QUANTITATIVE TOTAL FOOD ALLOWANCE FOR ONE DAY

(Carbohydrate, 61; protein, 73; fat, 30; calories, 802)

<i>Food</i>	<i>Gram weight</i>	<i>Household measure</i>
Bread.....	10.....	$\frac{1}{2}$ thin slice
Butter.....	3.....	$\frac{1}{4}$ square
Salad dressing with oil.....		
Milk (skimmed).....	400.....	2 glasses
Cream, 20 per cent.....		
Cream, 40 per cent.....		
Meat (lean).....	90.....	1 large serving (3 oz.)
Meat (low in fat).....	90.....	1 large serving (3 oz.)
Egg whites.....	66.....	2
Egg.....	50.....	1
Vegetables, 3 per cent.....	225.....	3 small servings ( $1\frac{1}{4}$ cups)
Vegetables, 6 per cent.....	75.....	1 small serving ( $\frac{1}{2}$ cup scant)
Fruit, 5 per cent.....	100.....	1 serving
Fruit, 10 per cent.....	200.....	2 servings
Vegetable and fruit, 15 per cent.....		
Vegetables and fruit, 20 per cent.....		

## SUGGESTED DISTRIBUTION OF THE TOTAL FOOD ALLOWANCE FOR ONE DAY

	<i>Breakfast</i>	<i>Grams.</i>
Fruit, 10 per cent.....	1 serving.....	100
Egg.....	1.....	50
Egg whites.....	2.....	66
Bread.....	$\frac{1}{2}$ thin slice.....	10
Butter.....	$\frac{1}{4}$ square.....	3
Beverage—coffee or tea.....		

### *Luncheon*

Meat (low in fat).....	1 large serving.....	90
Vegetable, 3 per cent.....	2 small servings.....	150
Fruit, 5 per cent.....	1 serving.....	100
Milk (skimmed).....	1 glass.....	200

### *Dinner*

Meat (lean).....	1 large serving.....	90
Vegetable, 6 per cent.....	1 small serving.....	75
Salad—vegetable, 3 per cent.....	1 small serving.....	75
Fruit, 10 per cent.....	1 serving.....	100
Milk (skimmed).....	1 glass.....	200

(1000 Calories)

## QUANTITATIVE AND ESTIMATED QUANTITATIVE TOTAL FOOD ALLOWANCE FOR ONE DAY

(Carbohydrate, 61; protein, 71; fat, 52, calories, 994)

<i>Food</i>	<i>Gram weight</i>	<i>Household measures</i>
Cereal (dry)		
Bread. . . . .	10 .	$\frac{1}{2}$ thin slice
Muffin, soy bean. . . . .		
Butter. . . . .	15 .	$1\frac{1}{2}$ squares
Salad dressing with oil . . . . .		
Milk (skimmed). . . . .	400	2 glasses
Cream, 20 per cent. . . . .		
Cream, 40 per cent. . . . .		
Meat (lean). . . . .	180	2 large servings (6 oz. each)
Bacon. . . . .	5	1 slice, crisp
Egg. . . . .	50	1
Vegetables, 3 per cent . . . . .	225	3 small servings (1 $\frac{1}{2}$ cups each)
Vegetables, 6 per cent . . . . .	75	1 small serving ( $\frac{1}{2}$ cup each)
Fruit, 5 per cent . . . . .	100	1 serving
Fruit, 10 per cent . . . . .	200	2 servings
Vegetables and fruit, 15 per cent. . . . .		
Vegetables and fruit, 20 per cent . . . . .		

## SUGGESTED DISTRIBUTION OF THE TOTAL FOOD ALLOWANCE FOR ONE DAY

	<i>Breakfast</i>	<i>Grams</i>
Fruit, 10 per cent. . . . .	1 serving. . . . .	100
Bacon. . . . .	1 slice, crisp. . . . .	5
Egg . . . . .	1 . . . . .	50
Bread . . . . .	$\frac{1}{2}$ thin slice. . . . .	10
Butter. . . . .	$\frac{1}{2}$ square . . . . .	5
Beverage—coffee or tea		

*Luncheon*

Meat . . . . .	1 large serving. . . . .	90
Vegetables, 3 per cent. . . . .	2 small servings. . . . .	150
Butter . . . . .	$\frac{1}{2}$ square. . . . .	5
Fruit, 10 per cent . . . . .	1 serving. . . . .	100
Milk (skimmed). . . . .	1 glass. . . . .	200

*Dinner*

Meat. . . . .	1 large serving. . . . .	90
Vegetable, 6 per cent. . . . .	1 small serving. . . . .	75
Salad: vegetable, 3 per cent . . . . .	1 small serving. . . . .	75
Butter . . . . .	$\frac{1}{2}$ square. . . . .	5
Fruit, 5 per cent. . . . .	1 serving. . . . .	100
Milk (skimmed). . . . .	1 glass. . . . .	200

(1200 Calories)

## QUANTITATIVE AND ESTIMATED QUANTITATIVE TOTAL FOOD ALLOWANCE FOR ONE DAY

(Carbohydrate, 62; protein, 71; fat, 76; calories, 1216)

<i>Food</i>	<i>Gram weight</i>	<i>Household measure</i>
Cereal (dry)		
Bread . . . . .	10 . . .	$\frac{1}{2}$ thin slice
Muffin, soy bean . . . . .		
Butter . . . . .	40 . . .	4 squares
Salad dressing with oil . . . . .		
Milk (skimmed) . . . . .	400 . . .	2 glasses
Cream, 20 per cent. . . . .	15 . . .	1 tablespoon
Cream, 40 per cent . . . . .		
Meat (lean) . . . . .	180 . . .	2 large servings (6 oz.)
Bacon . . . . .	5 . . .	1 slice, crisp
Egg . . . . .	50 . . .	1
Vegetables, 3 per cent . . . . .	225 . . .	3 small servings ( $1\frac{1}{2}$ cups)
Vegetables, 6 per cent . . . . .	75 . . .	1 small serving ( $\frac{1}{2}$ cup scant)
Fruit, 5 per cent . . . . .	100 . . .	1 serving
Fruit, 10 per cent . . . . .	200 . . .	2 servings
Vegetables and fruit, 15 per cent . . . . .		
Vegetables and fruit, 20 per cent . . . . .		

## SUGGESTED DISTRIBUTION OF THE TOTAL FOOD ALLOWANCE FOR ONE DAY

	<i>Breakfast</i>	<i>Grams</i>
Fruit, 10 per cent . . . . .	1 serving . . . . .	100
Bacon . . . . .	1 slice, crisp . . . . .	5
Egg . . . . .	1 . . . . .	50
Bread . . . . .	$\frac{1}{2}$ thin slice . . . . .	10
Butter . . . . .	1 square . . . . .	10
Cream, 20 per cent . . . . .	1 tablespoon . . . . .	15
Beverage—coffee or tea . . . . .		
	<i>Luncheon</i>	
Meat . . . . .	1 large serving . . . . .	90
Vegetable, 3 per cent . . . . .	2 small servings . . . . .	150
Butter . . . . .	$1\frac{1}{2}$ squares . . . . .	15
Fruit, 10 per cent . . . . .	1 serving . . . . .	100
Milk (skimmed) . . . . .	1 glass . . . . .	200
	<i>Dinner</i>	
Meat . . . . .	1 large serving . . . . .	90
Vegetables, 6 per cent . . . . .	1 small serving . . . . .	75
Salad vegetable, 3 per cent . . . . .	1 small serving . . . . .	75
Butter . . . . .	$1\frac{1}{2}$ squares . . . . .	15
Fruit, 5 per cent . . . . .	1 serving . . . . .	100
Milk (skimmed) . . . . .	1 glass . . . . .	200



## A FEW SUGGESTED SUBSTITUTIONS FOR REDUCTION DIET

In the place of 10 Gm.  $\frac{1}{2}$  thin slice of bread, may have one of the following:

Skim milk.....	100 Gm....	1 glass
Vegetable, 6 per cent.....	100 Gm....	1 serving
Vegetable, 3 per cent.....	300 Gm....	2 servings
Fruit, 5 per cent.....	100 Gm....	1 serving
Fruit, 10 per cent.....	50 Gm....	1 serving

In the place of 10 Gm. butter, 1 square, may have one of the following:

Salad dressing with oil.....	10 Gm....	2 teaspoons
Cream, 20 per cent.....	15 Gm....	1 tablespoon

In the place of 60 Gm. of meat, 2 ounces, and 15 Gm. of cream, 1 tablespoonful, may have one of the following:

Egg.....	2	
Cheese, solid.....	40 Gm	2 1-inch cubes

In the place of 100 Gm., 10 per cent fruit, 1 serving, may have one of the following:

Fruit, 5 per cent.....	200 Gm....	2 servings
Vegetables, 6 per cent.....	150 Gm....	2 small servings
Vegetables, 3 per cent.....	300 Gm....	3 servings

## ACCESSORY FACTORS IN TREATMENT OF OBESITY

**Exercise.**—The amount of exercise should be increased, unless obesity is complicated by disease, in which exercise is contraindicated.

**Water Allowance.**—Water may be taken as is the habit of the individual. There is no reason to restrict water greatly unless the obesity is complicated by a disease in which limitation of water may be desirable.

**Thyroid Medication.**—Physicians cannot be too strongly cautioned against promiscuous and indiscriminate use of thyroid gland in the treatment of obesity, especially by the laity. The use of thyroid extract outside of the well-controlled advice of a physician is pernicious as it frequently leads to material cardiac injury when taken for long periods or in too large doses. If the physician can observe patients daily and can make frequent tests of basal metabolism it aids materially in reducing the weight rapidly, and under certain conditions may be safely employed.

**Dinitrophenol.**—The introduction of alpha-dinitrophenol into therapeutics by Tainter, Cutting and their collaborators has aroused much interest. The outstanding actions of the drug are sustained increases in metabolism and body temperature with enormous activity of all metabolic functions.

Dinitrophenol is a very treacherous drug, and, at least for the present, should be used only as an experimental therapeutic measure in carefully selected patients under the close supervision of physicians who are familiar with the possible unfavorable reactions.

The original investigators feel that a daily oral dose of from 3 to 5 mg. per kilogram body weight is a safe therapeutic dosage. However, certain human beings have a variable and unpredictable susceptibility to its toxic effects. Its indiscriminate use by the public has already lead to fatalities. Physicians who administer the drug should inform the patient concerning the dangerous symptoms such as: increased temperature, severe urticaria and pruritus; and advise immediate discontinuance of the drug with any suspicious symptoms.

### CONCLUSIONS

The problem of obesity is difficult to solve perhaps because, as DuBois has stated, there is no stranger phenomenon than the maintenance of a constant body weight under marked variation in bodily activity and consumption of food. Few scientific data are available to explain maintenance of normal weight. Many factors, such as disturbance of endocrine glands, water metabolism, specific dynamic action, and fluctuations in basal metabolism, have been held responsible. Such data as Newburgh has recently presented in determining the total heat elimination and total water exchange, with accurate studies of the nature of obesity, do not lend support to the conception of a mysterious economy practiced by the tissues infiltrated with fat.

Obesity can and does occur in patients without showing clinically any direct relation to intake of food. Whatever the mechanism of obesity may be, the clinical fact remains ap-

parent that 2 persons on the same intake may vary in response, one getting fat and another remaining thin. My experience has led me to believe that underweight in the otherwise healthy person also occurs even when the intake of calories is more than sufficient to supply the demands of energy. The so-called "constitutionally" obese person and the healthy person who is underweight may present extremes of the same problem.

The difference between the so-called "exogenous" and "endogenous" types of obesity is only one of degree, not of kind, and both are the result of disordered metabolism which, in the last analysis, is probably due to some glandular dysfunction which alters the previous relation between intake of food and expenditure of energy.



## CLINIC OF DR. ROBERT W. KEETON

RESEARCH AND EDUCATIONAL HOSPITAL AND DEPARTMENT OF  
MEDICINE OF THE UNIVERSITY OF ILLINOIS

### THE TREATMENT OF MALNUTRITION IN GENERAL PRACTICE

The order of the discussion:

- Changes in Weight.
- Nondestructive Weight Loss.
- Acute Destructive Weight Loss.
- Chronic Destructive Weight Loss.
- Vitamin B<sub>1</sub> and B<sub>2</sub> Deficiency.
- Vitamin B<sub>1</sub> Deficiency.
- Vitamin C Deficiency.
- General Considerations.

It is the purpose of this clinic to illustrate the importance of the application of the known laws of nutrition to the treatment of the sick. In the past the appetite has been considered a satisfactory guide for the individual to follow in the choice of food. Indeed there are many doctors who still adhere to this viewpoint. They point to the animals who go about the selection of their food under its dictates and they emphasize the animal's apparent freedom from disease. The dog feels badly and on one occasion refuses his food, on another he may be observed on the lawn eating grass. They say that the patient should be given equal privileges. In viewing such an analogy it should be remembered that the animal continues to live because he can find in his environment all the requirements for life. When one of these requirements ceases to exist, nature exacts her penalty and the species becomes extinct.

In the second place animals have had no opportunities to have their appetites perverted by false prophets. Even under the dictates of such a normal appetite the span of life of the animals is as a rule shorter than that of man. The futility of this viewpoint has become so evident that all of the great state universities have developed departments of animal husbandry.

If we apply this principle that the inborn instinct and appetite is an adequate guide in matters of nutrition to man, then the baby who has had no opportunity to have his appetite spoiled should best be able to select his food correctly. On the contrary every one now recognizes that one of the great triumphs of medicine has been the accurately controlled infant feeding as practiced by our present-day pediatricians.

The study of nutrition is just another chore that advancing medicine has placed on the shoulders of the already overburdened practitioner, but let us face the issue for the study of the subject will yield large rewards in the treatment of patients.

### CHANGES IN WEIGHT

The lay public is quite familiar with the grave significance that is to be attached to a sudden change in weight. If there has been a sharp weight loss, they seek the doctor. If they have gained weight they may take a more philosophical view and regard it as a sign of advancing years. They have been educated to this viewpoint by the refusal of life insurance companies to accept as risks individuals who have recently undergone marked weight changes. As DuBois has put it, "There is no stranger phenomenon than the maintenance of a constant weight under marked variation in bodily activity and food consumption." He has calculated that the maintenance of this constant weight by a man over a period of twenty years involves an adjustment of food intake to total energy expenditure with an accuracy of 0.05 of 1 per cent. "This is an extraordinary exactness which is equalled by few mechanical devices and almost no other biological process."

Increases in weight are not often associated with serious

disease processes and because of the limitation of space the discussion of this class of cases will be omitted.

### NONDESTRUCTIVE WEIGHT LOSS

Weight loss occurs when for any reason expenditure of energy exceeds the supply derived from the food. If an individual is subjected to undernourishment he must secure the extra energy from his body. As long as he has stores of fat (deposit fat in the body) these will be utilized and his body proteins will be protected. This principle is utilized in the dietary treatment of obesity. If sufficient protein is fed to satisfy the appetite and enough carbohydrate to meet the requirements for antiketogenesis and the protection of the liver, the individual may lose weight without symptoms. It may first be called to his attention by the fit of his clothes or the observations of his friends. It is a not uncommon experience to have patients enter the office with such a symptomless weight loss. Our problem then resolves itself into finding the cause for the disparity between energy intake and expenditure. As a rule, we do not find a serious disease but we discover that the appetite has failed him. The weather may have been very hot, or he may have been upset by some unfortunate social or financial incident. With the loss of this regulator his knowledge of food values was not sufficient to enable him to select an adequate quantity of food.

**Case I.**—M. C., Hospital No. 49398. The patient is a white married female, thirty-three years of age, who enters the hospital complaining of:

Loss of 42 pounds in six months.

Attacks of asthma around her menstrual periods.

Fatigability and loss of appetite—four weeks.

The patient has had the attacks of asthma since twelve years of age. No infections or specific sensitizations were found to account for these. Since the attacks were more frequent around her menstrual periods she was given theelin and has been almost completely relieved.

During the last six months she has progressively lost weight and it was her opinion that she was eating well up to one month ago, at which time she became somewhat weak and lost her appetite. The detailed history developed no significant facts bearing on her complaint. The physical examination was negative except for an apprehensive attitude and cold moist hands. The laboratory studies showed no cause for the weight loss.

It seemed probable that the patient was not eating sufficient food and this was tested in the following manner. Her activity was reduced to a known amount by confining her to bed with bathroom privileges. She was next fed a quantitative diet. Experience has shown that a normal individual subjected to this amount of activity will maintain his weight on a diet containing calories 30 per cent above the basal requirements.

Her basal requirements were 1320 calories and the diet which was served to her contained 1718 calories ( $B + 30$  per cent). Her weight at the beginning of a seven-day period was 109 pounds and at the close 111½ pounds. The significance of this experiment was explained to her and she went home convinced that she only had to eat more food in order to stop the weight loss. With the added food the appetite improved and the fatigability disappeared.

#### ACUTE DESTRUCTIVE WEIGHT LOSS

**Case II.**—J. S., Hospital No. 48681. The patient is a tall white unmarried female, twenty-three years of age, who was sent to the hospital by her physician with a diagnosis of myasthenia gravis. Her complaints were:

1. Loss of strength in arms and difficulty in walking due to weakness.
2. Incontinence of urine and feces.
3. Huskiness of voice.
4. Loss of 25 pounds.
5. Insomnia.
6. Numbness in lumbar regions, buttocks, vagina and urethra.



The patient has never been a strong girl. She had rheumatism every winter from the age of twelve to twenty-one, but she has been able to remain employed as a factory worker. Her past history was not remarkable otherwise.

Two months ago she began having severe dysmenorrhea. She was forced to quit work, go home and remain in bed with heat applied to abdomen. During this time nausea was a prominent symptom. A friend of hers recommended two naprapathic doctors (husband and wife) who were successful in treating such conditions. She entered their hospital where she remained three weeks and received the following treatment:

1. Daily irrigations of bladder.
2. Daily colonic flushings.
3. Rubs with alcohol, and massage.
4. Heat to abdomen.
5. Special diet. This deserves careful study, for the first week she received water only, for the second raw fruit juices and for the third carrot salad and other "healthy foods."

During the periods in which she was being massaged and irrigated she received a liberal education in the various parts of her anatomy and special dietary instructions were given which could be followed on her return home. She was impressed with her physical inferiority and the necessity for continuing the treatment rigidly. Five days after her discharge from the naprapathic nursing home she was so weak that she called in a physician who sent her to the Research Hospital with a diagnosis of "myasthenia gravis."

**Physical Examination.**—The examination reveals a slender white female who shows evidence of a marked loss in weight. She has a sad weary expression with a faint icteric tinge to her sclera and a dry skin. She is obviously weak and trembles badly. Her voice is husky and she is so disturbed by the examination that she has difficulty in remaining quiet. Her weakness was so great that she could not walk any distance unsupported and she had difficulty in rising from the lying to the sitting position. The heart was rapid. The reflexes were all physiological and sensation was preserved. There

were no cranial nerve palsies and no difficulty in swallowing. The nurse's notes reported that during the early period of hospitalization she had both *urinary and fecal incontinence*. On vaginal examination hyperesthesia was noted and a *Trichomonas vaginalis* infection was found. The examination otherwise was not significant.

**Laboratory Studies.**—The laboratory studies consisting of blood counts, blood calcium, phosphorus, nonprotein nitrogen, CO<sub>2</sub>, sugar, cholesterol, Wassermann showed no abnormalities. The icteric index had a value of 16 and the urine gave a positive test for urobilinogen for five weeks after her admission to the hospital. The creatine output in the urine (0.6 Gm. per day) on admission was somewhat higher than it was later (0.45 Gm.) when she was taking adequate quantities of food.

**Diagnosis.**—At the time of entrance, the extreme loss of muscle power was striking. However, the cranial nerves were intact. Hence a diagnosis of "myasthenia gravis" was rejected and that of "acute inanition" was adopted. This opinion was confirmed by the neurological consultant.

**Treatment.**—The treatment that was to be followed was obvious but it was difficult because we were unable to secure her cooperation. For several days she ate poorly and offered unsatisfactory explanations of her conduct. It was evident that the naprapaths had instilled into her so many false ideas that a psychiatric consultation was imperative. In the course of two rather extended conferences she unburdened herself of her problems and conflicts. These were easily solved and she at once adjusted herself to the task of eating her way back to health. From now on the problem was a purely medical one.

She presented three outstanding pathological-physiological manifestations.

1. At the outset she had little or no stored fat (reserve calories). When the food was reduced below the maintenance level she secured her energy from the oxidation of proteins (body muscles). To this is to be attributed her emaciation and muscular weakness. The evidence of this destructive action

was found in the increased urinary creatine output. This is the classical picture described in textbooks of physiology and nutrition when lean animals or lean men are subjected to fasting experiments.

This destruction of muscle protein is easily stopped by the addition of sufficient calories to the diet. Up to a certain point, calories arising from carbohydrates are more efficient than those coming from fats.

The patient not only had the problem of stopping the destruction of body muscles but she was confronted with the necessity of rebuilding the muscle fibers requisitioned for fuel. This would come gradually from a surplus food intake. We endeavored to shorten this process by feeding glycine (amino-acetic acid). Glycine has been found to be a valuable agent in restoring muscle function in myasthenia gravis and it was used for this reason. The results seemed to justify its use. The patient's sense of strength and her endurance apparently increased sharply after 15 Gm. were added to her daily diet.

2. The heart muscle evidently had suffered somewhat as the result of the inanition. The rate was rapid (143 per minute) and the electrocardiogram showed evidence of alteration in muscular behavior, slurring of QRS, low voltage, diphasic T 2 and 3. Dyspnea developed rather readily. It was felt that measures used to restore voluntary muscular power would be equally valuable for the cardiac muscle. In addition to this, the patient's activity was reduced by making her an absolute bed patient.

3. This patient's liver was damaged by the starvation process. The evidence of this was found in subicteric tint to the sclerae, the yellow cast to the skin, the increase in icteric index (16) and the presence of urobilinogen in the urine. On admission this was reported as ++++ and one month later as +. It seems that an indispensable amount of stored carbohydrate is necessary for the liver function. When this is absent fatty degenerative changes are induced. When urobilinogen appears in the urine during a period of undernutrition the author believes that this is evidence that the indispensable carbohydrate moiety has been exhausted.

To correct this problem the patient was fed in addition to her hospital tray 100 Gm. of glucose dissolved in orange juice. This was served in four portions and did not interfere with her appetite for other foods. She was able to leave the hospital after fifty-three days in a fair state of nutrition with good muscle power.

#### CHRONIC DESTRUCTIVE WEIGHT LOSS

It is more usual to find destructive weight loss appearing in a chronic form. A group of illustrative cases will be presented.

**Case III.**—E. P., Hospital No. 43977. The patient, a white married female, twenty-one years of age, enters the hospital on a stretcher with a diagnosis made by her physician of Simmonds' disease. Her complaints are:

Irregular menstruation for years.

Pain in the abdomen and back—eighteen months.

Loss of weight—35 pounds in eight months.

Paralysis—two months.

Huskiness of voice to aphonia.

Difficulty in swallowing—two months.

The patient is a girl who has been frail most of her life, her best weight being 115 pounds. She has been the favorite child in the family and has depended on her mother in difficult situations. She dates her first illness of any consequences to November, 1933, one and a half years ago. At this time she developed pain in the abdomen and back which symptoms were attributed to "gravel in kidney." Recovery occurred in two to three weeks and she remained well until her marriage in September, 1934, nine months prior to entrance to hospital.

One month later she had a return of symptoms of 1933. These gradually disappeared but she complained of extreme fatigue and weakness, spending a good portion of her time in bed. At this time the weight loss began and the lower abdominal pains bothered her more and more. Medicine for relief of pain was used. The appetite disappeared and her intake of food diminished.

In April, 1935, two months ago, she rather suddenly developed an almost complete paralysis. She could not feed herself or sit up in bed. She lost rapidly the power to move in bed, and by June 12, 1935, the date of her admission, she was able to swallow only with great difficulty. Her voice was reduced to a whisper. She could manipulate her fingers somewhat, but was unable to shrug her shoulders, or move her arms or legs.

Prior to her loss of muscle power she had numbness and tingling in the hands and feet. The history otherwise was not significant.

*Physical Examination.*—The examination reveals an emaciated female, weighing approximately 60 pounds, who lies helpless in bed and speaks with difficulty in a whispered voice. The general physical examination shows the following significant findings.

Face: dusky pigmentation, no areas of pigmentation in mouth, axilla or inguinal regions.

Heart: embryocardia.

Cranial nerves: bilateral facial weakness. Fundi normal.

Motor: profound weakness of all extremities with wrist drop, foot drop, profound emaciation but no localized atrophy.

Sensory: vague peripheral hypalgesia, vibration sense good.

Reflexes: biceps, triceps, knee jerks and ankle jerks not elicited. Babinski plantar flexion.

Mentality: patient is alert.

*Laboratory Studies.*—Blood: nonprotein nitrogen 31, chlorides 424, glucose 94, CO<sub>2</sub> 54, serum albumin 3.10, serum globulin 1.34, icteric index 12, Wassermann and Kahn negative, white blood corpuscles 6600, red blood corpuscles 5,300,000, hemoglobin 15 Gm. Differential normal.

Spinal fluid: clear. Pandy negative. Pressure not increased, no block, Wassermann and Kahn chloride negative, cell count 8.

Urine: a few pus cells, trace of albumin, positive test for urobilinogen which persisted for two months.

The diagnoses considered in this case were Simmonds' disease, extensive poliomyelitis, Landry's paralysis (infectious myelitis) and peripheral neuritis. A diagnosis of "peripheral neuritis" due to starvation and avitaminosis was accepted largely because of the paresthesias which preceded the onset of the paralyses, the uniformity of the wasting and the paralytic process, and the history of the patient's lack of food intake.

*Treatment.*—The first consideration was the necessity for supplying the patient with adequate food. She had difficulty in swallowing and her physical reserve had reached such a low state that it was imperative to avoid undue exertion. Hence a nasal catheter was passed and she was given small quantities of liquid feedings into her stomach by a syringe at hourly intervals.

Diet				
<i>Foods in grams.</i>		<i>Carbo- hydrates.</i>	<i>Pro- teins.</i>	<i>Fat.</i>
Milk.....	1450	72.5	43.5	50.7
Cream.....	450	18.0	13.5	90.0
Orange juice.....	200	24.0	2.0	
Eggs.....	2	..	12.0	12.0
Sugar.....	40	40.0		
Glycine.....	15	...	15.0	
Yeast.....	4	3.0		
		157.5	86.0	152.7
Calories—2344				
Glucose—222.1				

The patient was in a state of starvation, a factor which had reduced her metabolic rate 20 per cent. She was paralyzed which prevented her from moving in bed, reducing her energy requirements further. For the bed activity of even a comfortable patient caloric requirements may reach a value of 15 per cent. Finally even under basal conditions there is considerable contribution to the basal requirements by the energy expended in maintaining muscle tone. It is safe therefore to state that her energy requirements were 40 to 50 per cent below those for a normal person of her size. The basal

requirements of such a normal person would amount to 2500 calories. On the basis of the above calculation this patient would not be using over 600 calories. One can now appreciate how she has been able to live in the face of what amounted to a three months' starvation period. The diet which was fed her by tube contained 2344 calories and was four times the amount expended on her admission to the hospital.

The tube feeding was continued for ten days. At times she regurgitated and vomited so that it was impossible for her to retain the full quota of food. At the end of this period she was strong enough to take food by mouth at frequent intervals. Progress was satisfactory for eighteen days until the intern who had taken care of her was transferred to another service. She at once began to fret and make all sorts of complaints. She lost her appetite and took her food poorly. At this point the nasal catheter was introduced and feedings continued. With the passage of a week's time and the assistance of the nasal catheter, she was able to forget her attachment to the intern sufficiently to return to oral feedings.

About five weeks after her admission she again was badly upset when her husband failed to pay her an expected visit. Loss of appetite and vomiting followed. The nasal catheter cured this in three days.

After a three months' stay in the hospital she was discharged with recovery advanced sufficiently so that she could move freely in bed, and feed herself with some assistance. There were a number of conferences between her and the psychiatrist. At the conclusion of these conferences it seemed quite evident that the patient was physically and mentally inadequate to meet her problems.

The sequence of events which led to the condition presented on entrance to the hospital may now be reconstructed. An attack of cystitis which would not have disturbed an ordinary person put her to bed for two weeks. She then became tired out and found it easier to remain in bed than to be up. It was easier to eat little or nothing, an inadequate diet, than to get up and prepare adequate food. Various neuritic pains

appeared for which she took medicine and continued to eat inadequately. Finally the full picture of emaciation and paralysis appeared. It was so extreme that her physicians made various incorrect diagnoses and she was passed from one to another as a hopeless case of Simmonds' disease. It is interesting to note that the correct diagnosis of peripheral neuritis on the basis of avitaminosis was made by the intern at the close of his careful history and physical examination. Again I wish to emphasize the fact that there is no substitute for a careful history and examination of the patient if correct diagnoses are to be made.

**Case IV.**—H. R., Hospital No. 36346. The patient presents an extreme degree of weight loss induced by ill-advised methods of weight reduction and the lighting up of a fatal disease.

The patient, a thirty-four-year-old female, was well but obese until May, 1933, at which time she undertook a reducing régime. She took daily a dose of saline cathartics which she saw advertised and which was purchased at a drug store. The salts spoiled her appetite so that she could not eat. The food was gradually restricted to one meal per day consisting of cheese, coca-cola and soda pop. The use of the salts was continued until Thanksgiving at which time she could retain no food. About January 1st (six weeks prior to admission), she vomited even water. Since January she has had a productive cough and she has suffered from numbness of the fingers and toes. Her total weight loss has amounted to 150 pounds in eight months. The patient continued to vomit after admission to hospital; the food was returned immediately after it was eaten. x-Ray of esophagus showed the typical cigar-shaped shadow seen in cases of cardiospasm. The sputum was large in quantity, offensive in odor, contained fusiform bacilli and spirochetes. Just prior to death tubercle bacilli were found. x-Ray showed multiple cavitation in the upper and lower lobes of the right lung. The course was steadily downward in spite of all therapeutic measures (nasal oxygen, nasal catheter feeding, therapeutic pneumothorax).



On autopsy the large cavities in the right upper and right lower lobes were found associated with numerous other small areas of abscess formation. The peribronchial glands were enlarged, soft and apparently seminecrotic. It is interesting in this connection to note that the Mantoux test gave a strongly positive test with an area of actual necrosis in the center.

This is a most instructive case because it shows the very great importance of the food elements in the body's resistance to disease. There was a maximum of exudation and transudation. The migration of organisms through the blood vessels and tissues was unimpeded. The picture in the lung was that of spontaneously developing areas of liquefactive necrosis. The entire lungs and lymphatic system were undergoing solution comparable to the melting of ice. It would be a highly speculative procedure to assign to any particular food element responsibility for resistance to infection, but the dissolution of this patient's body was accomplished by the simple process of withdrawing adequate quantities and kinds of foods.

#### VITAMIN B<sub>1</sub> AND B<sub>2</sub> DEFICIENCY

Case V.—E. M., Hospital No. 42573. In this patient the weight loss was not so marked but the destructive effect on the body was none the less significant.

This sixty-two-year-old woman entered the hospital on March 12, 1935, and told this story. She became sick in June, 1934, but a physician was not consulted until October, 1934, and no medicine was taken prior to that time. At the onset there was numbness, pain and swelling in the hands and feet. Her physician made a diagnosis of arthritis and prescribed cinchophen. The patient's condition grew steadily worse, her activities were reduced by the pain. On entrance she had not only swelling of the hands and feet but she was also dyspneic and orthopneic and in a low-grade state of confusion and delirium. A diagnosis was at once made of "multiple peripheral neuritis" but we were uncertain as to the etiological agent. Since the process was so painful, arsenic

was suspected. Her medicines were checked but none of them contained arsenic. The hair contained only a small amount. However, she was given sodium thiocyanate intravenously without improvement. So this diagnosis was abandoned. One next considered an alcoholic neuritis or alcoholic pellagra. She not only had extreme pain as noted above but she developed a severe diarrhea as soon as food and oral medications were begun. The patient and her husband both denied the use of alcohol in any form, but they admitted that for six months prior to the onset of her symptoms, they had lived on reduced rations of food. They were too proud to go on relief and were trying to weather the storm alone. Now that it has been established that the cases of alcoholic pellagra are due to dietary deficiency, the patient preferring to drink alcohol rather than to eat, it is easy to ascribe a painful multiple neuritis to avitaminosis directly without the necessity of invoking alcohol as an etiological agent. This patient may therefore be classified as deficient in both  $B_1$  and  $B_2$ .

Because of the irritable gastro-intestinal tract, it was necessary during the early stages of her hospitalization to resort to intravenous injections of fluid to protect her water balance. When the diagnosis became clear, she was at once placed on intramuscular injections of liver extract, a form of therapy which has been found valuable in alcoholic pellagra. Improvement was progressive and rapid. Later physiotherapeutic treatments gave her great comfort.

#### VITAMIN $B_1$ DEFICIENCY

**Case VI.**—M. S., Hospital No. 48221. The patient is a sixteen-year-old girl who has spent her life on a farm. She entered the hospital March 3, 1936 with the following complaints.

Swelling, discoloration and gangrene of both feet—one month.

Expectoration of clotted blood at irregular intervals for two years.

Swelling of fingers—four months

Her health was fair until December, 1934. At this time swelling of the feet and ankles appeared in the morning and became progressively worse so it was difficult to get her shoes on by evening. There was a purplish discoloration of the feet and ankles and a loss of feeling. She went to bed and remained there until May, 1935. Contrast baths were tried but discontinued because of the pain. Various types of ointments and salves were ineffectual.

In spite of an alleged good appetite during her five months in bed she lost 25 pounds. In May, 1935, she became more active, the color of her feet improved and swelling decreased. Throughout the summer she felt tired and lacked energy. In November, 1935, the feet again became swollen and purple, especially the toes. The skin over the feet became hard and felt "petrified." Intermittent pains appeared in the toes. The small toe of left foot turned black and was removed one week ago. In January large blisters developed on both feet which discharged a bloody fluid at times, at other times a straw-colored fluid. More recently (five weeks) the fingers became purplish with white round hard tips. She denied having had frostbite at any time.

Two years ago she began spitting up thick bloody clots in the morning at four- to six-week intervals. At this time she bled from the nose also. On further questioning she states that she has had a good appetite and has eaten well. There is no history of the development of bilateral blanching of hands or feet on exposure to cold.

The examination reveals a girl who is fairly well-nourished but much underdeveloped for her age (sixteen). She had the appearance of a child eleven years of age. She is not in any acute pain. The hands and feet have been described. There is a lack of hair and development of secondary sexual characters.

The neurological examination showed the cranial nerves normal except for an internal strabismus on the right side. The upper extremities were normal as regards sensation, power, tone and reflexes. There is weakness of the dorsiflexion of

ankle, plantar flexors of ankles, and corresponding weakness in the toes. Knee jerks increased, ankle jerks normal. Flexion to Babinski, calves tender, Achilles tendon quite tender. Patient cannot walk on heels with toes off the floor. Plantar surfaces hyperesthetic, trophic ulcers on feet.

The laboratory studies were complete.

Blood, hemoglobin 12.3 Gm., red blood corpuscles 4,820,000, white blood corpuscles 7.6, differential normal, coagulation time ten minutes, bleeding time six minutes, clot retracts normally, platelet count 340,000.

*Blood Chemistry.*—Glucose 90, nonprotein nitrogen 40, CO<sub>2</sub> 52, cholesterol 222, calcium 9.2, phosphorus 6, Wassermann and Kahn, negative.

Oscillographic studies showed normal findings for both legs.

*x-Ray Studies.*—Right foot showed decalcification which is probably in the nature of secondary atrophy due to disuse or trophic disturbances.

Lower spine no pathology such as a spina bifida.

Chest negative.

Biopsy of leg muscle showed normal vessels.

*Diagnosis.*—Raynaud's disease was eliminated because there was no history of intermittent blanching of feet and hands on exposure to cold.

A very early onset of hypertensive disease was ruled out by the normal oscillographic response and the normal microscopic appearance of blood vessels in the biopsy.

Trophic changes in feet secondary to a vertebral anomaly was eliminated by x-ray plates of spine.

Since the patient had evidences of bilateral muscle weakness, trophic changes (gangrene and blebs), tendon tenderness, hyperesthesia of plantar surfaces, a diagnosis was made of "peripheral neuritis" probably due to lack of antineuritic vitamin.

*Treatment.*—She was continued on ward diet and given brewers' yeast, 6 Gm. per day. Her recovery began at once and was completed at the end of three months when she was discharged.

This case is extremely interesting since it records a case of vitamin B<sub>1</sub> deficiency in a young child who has been reared on a farm where presumably there was an abundance of foods containing the antineuritic vitamin.

#### VITAMIN C DEFICIENCY

**Case VII.**—L. M., Hospital No. 47499. Present complaints: vomiting—three years.

Lower abdominal cramps—three years.

Localized pain in left upper quadrant.

Hematemesis—four months.

Epigastric pain—four months.

She had stomach trouble off and on all her life. At age of fourteen years she almost drowned and since then her troubles have increased. Chronologically the events may be summarized.

Age sixteen, 1931 appendectomy, recovery poor; remained in bed for six months.

Interval of activity three months' duration, terminated by vomiting, returned to bed for six months, at end of which time a diagnosis of pulmonary tuberculosis was made. Entered sanatorium in fall of 1932 and remained a patient until January, 1936, except for a short period when she was in hospital for surgical treatment. During the period of sanatorium care she has had a continuous abdominal problem. At times this was characterized by cramps and vomiting, at other times diarrhea and bloody stools. In 1933, an abdominal exploration was made and a portion of bowel removed because of tuberculous enteritis. In 1934 tonsils were removed. In September, 1935, the vomiting increased to the point at which she lost 2 meals per day. In November, hematemesis of small amounts began and has continued to the present. There is also associated with this bloody bowel movements. She enters the hospital on diet management consisting of milk and cream and alkaline powders.

The physical examination reveals a young white female whose previous weight has been 115 pounds, whose expected

weight is 130, but whose actual weight is 87 pounds. She hiccoughs persistently during the examination and has vomited one time. She looks worried and complains chiefly of abdominal pain and soreness. The examination except for the abdomen and general appearance was not remarkable and will be omitted. The gums were in fair condition and were not bleeding and did not contribute the blood to the sputum.

*Laboratory Studies.*—Urine, acetone ++, albumin trace, urobilin 0.

Stools, blood ++.

Blood, hemoglobin 11.2 Gm., red blood corpuscles 4,000,000, white blood corpuscles 4400, platelets 250,000 differential normal, leukocyte count later dropped to 9850, hemoglobin remained unchanged. Wassermann negative.

Chemistry, normal limits.

Sputum, negative for tuberculosis and Vincent organisms.

*x-Ray.*—Chest, increase in shadows of hilum no parenchymal changes.

Genito-urinary tract, esophagus negative. No organic lesion, irregular distribution of barium in intestine with formation of isolated masses suggestive of intestinal adhesions and spasticity.

Barium enema, no obstruction or filling defects. Kidneys, intravenous pyelograms, no apparent pathology. Proctoscopic examination—no ulcerations or pathology up to 25 cm.

Esophagoscopy—no pathology and no indication as to source of bleeding.

*Diagnosis.*—The diagnosis in this case offered many possibilities. She was sent to the Research Hospital by her physician on the assumption that she had an intractable tuberculous enteritis and that an intestinal obstruction was imminent. It was felt that the case was one that would require surgery. One had only to read this patient's history to realize that we were dealing with a food deficiency. She might have tuberculosis but there could be no doubt that her diet was inadequate in calories and in other essentials. Hence it seemed wise for the time being to fix our attention on the nutritional problem. This

view was further justified when no ulcerations were seen in the esophagus and rectum and no organic diseases of stomach was revealed by x-ray. The bleeding was attributed to a capillary disease since the platelet counts and bleeding time were normal. Since vitamin C (ascorbic acid) regulates the colloidal conditions of intercellular substances, it was clear that among other things, we were dealing with a deficiency in this vitamin.

*Treatment.*—The management of this patient taxed our ingenuity and patience to the limit. The plan followed will be briefly summarized:

1. By repeated interviews on the part of the house officers, she was persuaded that she had a chance to get well providing she would cooperate. This was not an easy task since we were dealing with a young girl who had been bedridden from sixteen to twenty-one years of age, had spent four years of this time in a sanatorium for tuberculosis and had been subjected to 3 surgical procedures of questionable value (appendectomy, resection of bowel and tonsillectomy).

2. The fluid balance at first was maintained by almost daily injections of 5 per cent glucose in buffer solution.

3. Blood transfusion.

4. Utilization of all the known tricks to keep her from vomiting.

5. The daily or every other day intravenous injection of ascorbic acid (vitamin C) in 100- to 200-mg. doses.

The bleeding stopped within a short time of the use of the ascorbic acid. Her pain subsided and she left the hospital at the end of four months, eating the ward diet and with a gain of 8 pounds.

#### GENERAL CONSIDERATIONS

If, in treating the sick, one can keep before him the conception that there are certain indispensable requirements for the proper functioning of the body and that these must be met in sickness more rigidly than in health, he will have a most valuable aid in therapy. He will find that many symptoms

presented are not necessarily a part of the disease but they may be due to the neglect of some of the common laws of nutrition. If these are corrected the disease loses its terrors. The great outstanding contribution of this nature was made by Coleman in 1912 when he described the treatment of typhoid fever patients with high calorie diets.

Suppose we consider for the moment the symptom of incontinence of urine, urinary retention and incontinence of feces. When such symptoms are mentioned to a physician he at once begins to think of a serious disease process, and yet I have been struck by the frequency with which these occur in such cases as I have been describing. All of the patients who have entered the hospital with profound undernutrition and wasting have had incontinence of urine and feces, and have recovered from these by being fed. Time does not permit me to cite the details of the records of 2 other cases suffering from malnutrition who had urinary retention. Both of these patients were submitted to cystoscopic studies and there were no evidences of obstruction found and there was no cord bladder present. When they were in nutritional balance the bladder functioned perfectly. After all the disease or infection may be producing its symptoms by destroying vitamins or interfering with their function. It is logical to believe that the vitamin in question might be furnished in such large doses that the infection could not completely rob the body of its action. Then the patient would be relieved of his annoying symptom in spite of the fact that he may not be cured of the disease. From this viewpoint the physician would be constantly bending his energies toward the objective of keeping the bodily processes functioning physiologically rather than allowing them to become pathological.

It would seem unwise to close this discussion without calling attention to the large psychic element in nutrition. The vegetative mechanism is constantly subjected to reflexes originating in the mental field. If these are pleasurable, there is a facilitation of digestion, if they are not there is inhibition. A disturbing bit of news is received and the individual loses



his appetite, if the adjustment is difficult he may become nauseated and vomit. One has only to look at the nervous worried patients who are suffering from anxiety neuroses to realize the great blockade that the mind offers in these patients to maintenance of a normal nutritional state. We may force food on them, but we could accomplish our ends much better if the anxiety status could be removed.

The great majority of nutritional problems arising in the young spring from some abnormal psychic reaction. These may be the results of improper education or unfortunate circumstances, but rarely is the nutritional problem met until the psychic adjustment is made. Reference to the cases cited will show the large part played by the psychiatrist in their treatment.



## CLINIC OF DR. C. A. ALDRICH

### CHILDREN'S MEMORIAL HOSPITAL

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#### THE USE OF VITAMINS IN CHILDREN'S DIETS

It is quite natural that physicians interested in the care of children should have responded early to the implications resulting from the discovery of the various vitamins. because the most marked vitamin effects are upon the growing animals. Antagonism tinged with incredulity was the first reaction. later came gingerly acceptance, and the present attitudes range from extreme skepticism to extreme enthusiasm. The extent to which various clinicians use these accessory food factors in their actual work, therefore, varies considerably. It is the purpose of this paper to outline the known facts about their functions so that the reader may use his own judgment in making use of these therapeutic and preventive agents.

#### GENERAL GROWTH EFFECTS

It may be stated at the outset that practically all of the known vitamins seem to be necessary in order that general growth of the body may proceed. In view of the extremely small amounts necessary to permit of general growth, it is unlikely that they supply necessary building stones in the process. It seems more probable that they act as catalysts in the chemical processes characteristic of growth. It seems quite well established that the amount of growth is not quantitatively dependent upon the dosage of administered vitamins. In other words, the statural possibilities of an individual are not dependent upon quantities of vitamins in excess of those necessary to catalyze the growth reaction. This fact should make the physician skeptical about enthusiastic statements

made by experimenters as to increases in growth due to vitamins. In one extreme case I recall that an increased growth of 100 per cent was claimed to be due to treatment with vitamin B. This is manifestly impossible in normal animals, and if it were possible would be highly undesirable since there is considerable evidence to show that abnormally rapid growth tends to shorten the life span.

One would expect to find increased rate of growth as a result of vitamin feeding only when the test group of individuals was compared with a control group kept under conditions of vitamin deficiency.

#### EFFECTS UPON THE GROWTH AND FUNCTION OF SPECIFIC TISSUES

Even more startling than knowledge of this general growth-promoting function is the fact that each vitamin seems to have a specific influence on the histologic development and function of definite tissues. Therefore, in the case of each vitamin, it is possible to demonstrate pathologic lesions resulting from deficiency diets. In this field, the effect of vitamins is to a certain extent quantitative. The severity of the pathologic changes vary with the degree of the deficiency and its duration.

It is probably true that the function of many of the endocrine glands is related to specific vitamin changes, but this field of investigation has not yet been explored adequately. The parathyroids are known to be associated in function with vitamin D and the suprarenals probably complicate the problem of vitamin C. Many vitamin problems may be cleared up when their relation to hormones is understood.

#### VITAMIN A

Because it was for a long time unsuspected that there was more than one fat-soluble vitamin and because we did not realize that vitamin A could be synthesized in the body from its precursor carotene, accurate observations about this substance were delayed for many years. It has been definitely shown that it is essential for general growth and for life itself in

experimental animals. The following table summarizes the specific local changes found in vitamin A deficiency states.

- (a) Xerophthalmia and hemeralopia (night blindness).
- (b) Secondary infectious processes due to abnormal epithelium in the upper respiratory tract, lungs, glands and genito-urinary tract.
- (c) Renal lithiasis.
- (d) Sterility.

All of these changes are due primarily to keratinization of mucous membranes, which is the typical histologic lesion demonstrable.

Since it is true that vitamin A and its precursor carotene are liberally supplied by nature in ordinary foods, it is evident that absolute deficiency of this food factor probably does not occur in human beings. Under extreme conditions of fat deprivation such as may happen among poverty-stricken people and during wars, partial deficiencies may be fairly common. The eye conditions have been reported frequently from Scandinavian countries.

The most controversial point about vitamin A has been concerned with its relation to infectious processes. It was called the "anti-infectious vitamin" by many men and many observations substantiated this description. It was not until the demonstration of its mucous membrane effects, in preventing the development of keratinization, that the true function of this vitamin in preventing infections became clear. It now seems beyond reasonable doubt that protection from infection is not dependent upon any immunologic reaction in the blood or tissues but does result from the maintenance of normal mucous membranes.

It is easy to understand how the substitution of squamous cells could lead to local infections of considerable severity. Tyson and Smith list the following changes due to vitamin A deficiency: "metaplasia of cuboid or columnar epithelium in certain parts of the body, epithelial hyperplasia in various structures in this order; sublingual glands, submaxillary glands, epithelium of the renal pelvis and of the trachea and bronchi."

From a practical standpoint, the most important consideration today is whether or not prevalent "colds" are due in part to avitaminosis A. The question has not yet been satisfactorily answered in spite of considerable research, as many experiments have resulted in contradictory or equivocal findings. In my opinion the problem resolves itself into one of socio-economics, because the only type of people at all likely to be undernourished with this substance are those who are poverty-stricken. It may be of clinical importance that the babies of such people have a much higher morbidity and death rate from mucous membrane infections and their sequelae than is suffered by the young infants of the more privileged social groups. Since these poor mothers and babies often exist on diets containing very little vitamin A, it is conceivable that avitaminosis exerts a controlling influence here. At any rate it would seem but just to attempt an en masse improvement in the dietary supply of this factor in the poverty groups. Whether or not concentrates will be necessary or advisable awaits further knowledge as to dosage. From the standpoint of the baby's diet, much has already been accomplished in the routine administration of cod liver oil, an excellent source. The weak spot in our plan is found in the extremely poor prenatal diets eaten by most of the mothers.

The sterility which results from vitamin A deficiency is also produced by epithelial changes, keratinization of the membranes of the reproductive system. There is decreased or absent spermatogenesis in the male, whereas in the female the changes in the epithelium seem to make implantation of the fertilized ovum impossible. These abnormal conditions in both male and female are reversible so that adequate administration of vitamin A will restore the lost sexual function.

It is often forgotten that during lactation there is an increase in the need for this substance in the mother's diet.

It should be noted that mineral oils should not be taken at the same time that vitamin A is administered, because the fat-soluble vitamin is absorbed by the larger quantity of mineral oil and is thereby prevented from assimilation into the

body. More rarely, it has also been observed that certain abnormal intestinal and hepatic conditions have interfered with its utilization after it was thought that adequate dosage had been prescribed.

Summarizing the practical importance of this vitamin, then, it might be said that absolute deprivation is rarely possible in human beings because of its widespread distribution, but that partial deficiency is known to occur often enough to have made it a matter of considerable importance in certain countries under normal conditions and in many during wars and famines. Whether or not a relative deficiency of vitamin A is an important factor in the prevalence of mucous membrane infections and their more serious sequelae is yet to be determined. Adequate knowledge as to dosage is not yet available, but it is customary to assume that the amount found in three teaspoons of standard cod liver oil is a sufficient daily dose. The inclusion of cream, milk, butter and green vegetables in the diet should make concentrates unnecessary, in normal children.

#### THE VITAMIN B COMPLEX

In spite of the fact that one of the members of this water-soluble group of vitamins was the first to be isolated, the exact functions of these accessory food factors are less well known than are those of more recently discovered substances. There are probably several as yet undifferentiated members in this group, but at the present time it is possible to discuss intelligently only two, vitamin B<sub>1</sub> and G (P or B<sub>2</sub>). Vitamin B<sub>1</sub> is heat labile and G is heat stable.

#### VITAMIN B<sub>1</sub>

This has been called the antineuritic vitamin because polyneuritis is the best known pathologic state caused by its lack. Beriberi is the best known human disease resulting from avitaminosis B<sub>1</sub>, and is prevalent in oriental countries.

It has been amply demonstrated that animals on diets deficient in this vitamin do not grow normally, but whether or not this is due to pure avitaminosis is a controversial point. Many observers feel that the lack of growth observed is due

to inanition resulting from the anorexia which commonly follows diets deficient in vitamin B. In fact, it has been claimed that all of the pathologic lesions seen in B<sub>1</sub> avitaminosis can be duplicated in starvation.

The work of several observers indicates that the mental growth of young animals is retarded if their mothers were kept on deficiency diets during pregnancy. Unfortunately this condition seems to be irreversible, since the postnatal administration of the vitamin does not restore their mental function to normal.

Changes in the hematopoietic system are likewise found, but here again it is possible that inanition plays a rôle. It may be of significance in this regard that many of the newer liver extract preparations are found to be excellent sources of this vitamin.

The developmental changes include myelin degeneration of nerve fibers extending to voluntary muscles, degeneration of the fibers of Auerbach's plexus, focal lesions in the brain and pons, hypertrophy of the heart and suprarenals, and atrophy of the mucous and muscular layers of the stomach and intestines. Hemorrhages into the osteogenetic system seem to be a part of the picture. Consideration of these lesions will explain why some men have emphasized that this vitamin is of functional rather than of structural importance, and will explain the asthenia seen in some of these patients.

It has been demonstrated repeatedly that during lactation there is marked increase in the demand for vitamin B<sub>1</sub>. This is because the vitamin is not excreted quantitatively in the mother's milk.

#### VITAMIN G (P, B<sub>2</sub>)

While it is probable that in their relation to general growth and appetite this vitamin and B<sub>1</sub> are similar, other specific functions are quite different. In vitamin G deficiency, skin and mucous membrane lesions are found in addition to the nerve degenerations. In experimental animals, dermatitis, alopecia, stomatitis, glossitis, and cataract have been found due to deficiency of this vitamin alone.



There is still considerable controversy over the question as to whether or not pellagra is a pure avitaminosis G. or P. as those on the affirmative side choose to call it. Certainly the two conditions have been closely linked together. Pellagra can be prevented by administering vitamin G, and the disease frequently occurs in those living on diets poor in this factor. Treatment with the vitamin has been successful in those patients whose disease was of relatively short duration, but has been disappointing in those who have been ill for long periods of time. It is contended by those who defend the deficiency nature of the disease, that the nerve and cord degenerations resulting are irreversible changes so that cure after sufficient time has elapsed for them to take place is impossible under any conceivable management.

Summarizing the points of practical importance about the vitamin B complex it should be noted that the vitamins in this group are of primary importance in general growth and for the maintenance of a good appetite, at least in experimental animals. Without an adequate supply, degenerative nerve lesions develop centrally and peripherally. In addition beriberi and probably pellagra are caused by avitaminosis B.

While the dosage has not been adequately worked out on human beings, it is comparatively easy to administer these factors either in the normal diet by attention to the articles of food offered, or by the use of concentrates such as brewer's yeast tablets, carbohydrates with added vitamin B such as are advised in infant feeding, or in liver extract prescriptions. It is my personal feeling that, since no evidence has been offered that there is any likelihood of overdosage, its routine administration to young infants is indicated.

#### VITAMIN C

Although scurvy, the best known condition associated with vitamin C, has been recognized for many generations as a deficiency disease, this factor was among the last to be discovered. Nevertheless, recent chemical discoveries have compensated for the delay. Recognition of its exact composition

has resulted in making cevitamic acid available in pure form.

General growth and life itself are dependent upon a sufficient amount of this factor in the diet. After its elimination, experimental animals begin to lose weight in about ten days and usually die in from three to four weeks. Because it is an extremely difficult thing to find a human diet which is absolutely deficient in this vitamin, patients with scurvy have usually run a longer course than this before death.

All of the pathological changes found in vitamin C deficiency are probably dependent upon one fundamental lesion, capillary damage, a failure in the laying down of cement substance between the endothelial cells. In listing the various lesions seen one should include edema, serous effusions, hemorrhages into the skin, parenchymatous organs, bones and periosteum, cardiac hypertrophy, enlargements of the shafts of bones particularly at the metaphyses, fractures, epiphyseal separation, beading of the ribs, and degeneration of nerves.

Because of the similarity of the nerve lesions in avitaminosis B and C, many men believe that these two water-soluble vitamins are intimately related.

Since the isolation of cevitamic acid as pure vitamin C it has been possible to estimate its concentration quantitatively in the blood stream. This advance makes unnecessary the cruder attempts to demonstrate its deficiency such as the various capillary resistance tests.

Much work has been expended in trying to estimate the degree of importance which should be attached to this vitamin in regard to dental caries. Enough has been accomplished so that we know it to be a factor, but it is undoubtedly only one of the many concerned in this complicated problem.

Critical consideration makes it evident that because of its fundamental importance vitamin C should be considered in the arrangement of any diet. It is easily administered in fruit juices or raw vegetables. As a practical point which should be kept in mind in these days of evaporated milk's popularity, it should be repeated that a potent source of vitamin C should

be given all children on an exclusive cooked milk diet. It is not uncommon to see patients with scurvy in our children's hospitals nowadays because this fact is overlooked. While amounts as small as 1 or 2 teaspoons of orange juice have been known to cure scurvy, the optimal dose is probably several times as great. Most children tolerate from 3 to 4 ounces or more daily.

#### VITAMIN D

This factor did not emerge from obscurity until comparatively recently because it is associated in nature quite closely with vitamin A, and for many years their relative functions were confused. Thanks to the accurate observations of Melanby, McCollum, Huldshinsky, Hess, Steenbock and others, the importance of ultraviolet light in the genesis of this factor was discovered. As a result, activated ergosterol, known in this country as viosterol, can be produced in large quantities. This is a close approximation to, but is not a pure vitamin.

Because it is fairly well stored in the body, vitamin D may be eliminated from the diet for a considerable time before general growth is disturbed, but ultimately it has been found necessary for this process.

The local or specific lesions resulting from relative or complete deficiency are all due to insufficient delivery of calcium and phosphorus to the bones. The bones are soft and fragile and present various deformities most marked in the epiphyses where the most rapid growth normally takes place.

The exact pathogenesis of rickets, avitaminosis D, is still unknown, although it is recognized that in some way this vitamin assists the body in assimilating and retaining calcium and phosphorus so that their level in the blood stream is sufficient for normal osteogenesis.

When massive overdoses are given, thousands of times the average generally used, the amount of these minerals found in the blood stream may reach pathologic proportions and lead to untoward effects. This result can hardly occur, however, when doses approximating those usually prescribed are administered.

Tetany, since it is associated with a low level of calcium in the blood, is directly related to vitamin D.

It is also quite evident that an adequate amount of this factor is needed for the formation of normal teeth and jaws.

From a practical standpoint it is interesting that vitamin D in the form of cod liver oil had proved itself so valuable from a strictly clinical standpoint that its routine use was advocated long before it was known to exist as an accessory food factor. It is undoubtedly true that in all temperate climates vitamin D should be administered routinely to children, as exposure of the skin to ultraviolet light is usually insufficient to permit of normal absorption of the vitamin.

It is generally felt that from 1 to 3 teaspoons daily is the optimal dose. Various concentrates such as viosterol, cod and other fish liver oil concentrates, and various fish oils fortified with viosterol, flood the market so as to confuse even the best informed physicians. I can only advise that in considering the dose to be prescribed, these figures be translated into plain cod liver oil equivalents. In general, since cod liver oil has proved itself so valuable empirically, the more natural products should be preferred to those artificially prepared. During the summer months this factor may be discontinued if the body is exposed frequently to sunlight.

#### VITAMIN E

This substance was the last of the fat-soluble vitamins to be isolated. As yet it has not been shown an absolute necessity for general growth except in the fetus. It is unusually well stored in the body so that the experiments on this problem are hard to evaluate.

The importance of this food factor became evident when sterility was produced in experimental animals on diets which contained adequate amounts of the other known vitamins. It is an extremely interesting fact that the sterility which results is an entirely different process in male and female animals. It is due, in the male, to degeneration of the germinal epithelium. In females it is apparently a result of fetal death, as the

embryos are all absorbed. If a single large dose of the vitamin is administered early to pregnant animals, enough of the factor is stored to permit of normal gestation.

The degenerative changes found in the germinal epithelium of males are irreversible so that in most animals readministration of the vitamin does not restore their ability to impregnate. The secondary sex characteristics are not affected by this deficiency.

Sterility due to deficiency of vitamin E has not been shown definitely in human beings, but suggestive cases have been reported and it remains a possible cause.

### GENERAL CONSIDERATIONS

After reading such a résumé as this of the effects of the various vitamins, one's first response is confusion. One wonders how the race grew up when it was ignorant of all this startling knowledge. Such questions as to what degree avitaminosis was prevalent in past times, what vitamins are yet to be discovered, how many pathologic processes as yet of undetermined origin will be found due to deficiencies, and just what is a sensible attitude to take now, crowd into our thoughts.

The facts cannot be denied. Many important disease entities have been adequately explained and their treatment established. We must admit the importance of these substances for normal growth and life itself. Shall we then rush in and see to it that these substances in the form of known concentrates are routinely administered to children?

It seems to me that the lesson to be learned from all this is more fundamental. All of these substances are and have been freely available to human beings in the varied diets they naturally consume. It is inconceivable that the race could have evolved to its present point if the necessary factors for growth were not so easily available. The difficulty has arisen from our handling of the food stuffs. In our recent use of highly processed and cooked viands we can now see that many of the most important accessory factors are destroyed. It seems to the author that the thoughtful physician of today

must see to it that the children he cares for are taught to eat a wide variety of foods as little changed from their natural state as possible. In this way one would expect to supply adequate amounts of the known vitamins and also the ones which future investigators may discover tomorrow. Such a program will entail not only offering these foods to children but also considerable modification of adult diets because children will like to eat what they see others consuming. It will involve considerable attention to the growing appetites of youngsters. Fortunately most children like foods in a relatively unrefined state better than they do more sophisticated foods. Highly seasoned and sweet articles of diet should be withheld as long as possible from their attention.

The use of vitamin concentrates will be advisable for treatment of avitaminosis, but with the possible exception of vitamin D will probably not be necessary routinely if the general public will insist on a natural diet which is adequate. If the present tendency toward refinement of foods persists and carbohydrates remain as popular as they have been for the last fifty years, it is conceivable that routine administration of concentrates may become necessary.

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INANITION

INANITION or emaciation is a symptom due to starvation or to disease, or may be the result of both disease and starvation. The basic cause is an inadequate diet or the faulty utilization of an apparently satisfactory diet. The metabolism of absolute starvation has been studied in professional fasters and in experimental animals. These studies emphasize the fact that food is necessary for the preservation of life and that if it is not obtained the body tissues will be utilized. To protect these tissues the basal metabolism assumes a definitely lower level. The carbohydrate stored as glycogen and the "deposit protein" are oxidized first; then the body fat is drawn upon and finally, the body protein. The tissues of greatest physiological importance are spared as long as possible. When the most vital organs are sapped, death occurs.

Clinically we are concerned with semistarvation (incomplete inanition). This may be due to a diet inadequate in quantity or in quality, or deficient in both respects. Many functional disorders and pathologic conditions lead to impairment of appetite and an inadequate intake of food, or to faulty utilization of the diet. Diseases of certain endocrine glands which are fundamentally concerned with nutrition quickly lead to emaciation.

The following patients and case reports are presented to illustrate various types of inanition:

**Case I.**—This patient is forty-five years of age. Her height is 66½ inches and her weight 106 pounds. She has been an example of constitutional leanness, always underweight but able to carry on her duties as a nurse without undue fatigue. She married at forty years of age and since that time has kept house. The past year brought considerable nervous tension due to several deaths in her family and especially, to the unaccustomed care of an adopted child. She lost much sleep, developed anorexia and exhaustion, and lost weight. In the past six months the menses have been delayed and prolonged, but scant. Prior to admission to the hospital for a diagnostic curettage she flowed for five weeks. There have been no hot flashes.

Examination shows an emaciated woman with scaphoid abdomen. Her nervous facies suggests hyperthyroidism although there is no goiter clinically; her pulse is slow and tremor of the fingers is absent. Physical examination is otherwise negative. Blood pressure 130-80. Blood examination showed slight secondary anemia. Wassermann negative. Urine normal. Blood calcium 9.95 and cholesterin 294 mg. Of interest is the fact that on June 9th her basal metabolic rate was -41 per cent (weight 101½ pounds); on June 11th the basal metabolic rate was -27.9 per cent (weight 104 pounds); and on June 15th the metabolic rate was -16.3 per cent (weight 106 pounds). The change in the basal rate was due solely to bed rest, a high caloric diet and sedatives; no thyroid medication was used. In two weeks at home on rest periods, diet and iron, she has gained 7 pounds in weight and feels less fatigued.

**Diagnosis.**—Constitutional leanness; functional bleeding of the menopause; semistarvation due to anorexia from nervous causes, producing extreme exhaustion and a low metabolic rate.

**Case II.**—This patient, a lumberman, forty-five years of age, was admitted to the hospital because of weakness, loss of 40 pounds in weight, vomiting, a pressure distress in the epigastrium, and constipation. Weight 126 pounds, height 69 inches



Gastro-intestinal symptoms had been present for five years, but he had had remissions of as long as four months' duration. Symptoms appeared in the following sequence: constipation, belching relieved by induced vomiting; regurgitation of sour material which caused vomiting; a sensation of pressure in the epigastrium, relieved by vomiting. The belching and pressure occurred chiefly about two hours after supper and were apt to disturb him during the night. The symptoms gradually became worse. Six months before admission all of his remaining teeth were extracted; thereafter he subsisted on a liquid diet and during this period he lost 25 pounds in weight.

Examination revealed a muscular but emaciated, edentulous man. Blood pressure 90-60. The abdomen was distended: peristaltic waves, apparently of gastric origin, were observed. No masses were palpable and the liver and spleen were not enlarged. Thyroid normal. Heart and lungs negative. Moderate secondary anemia present. Wassermann negative. Aspiration of the stomach at 8:30 p. m. yielded 1000 cc. of food material; sarcinae were found. Stools contained no blood.

The attempt was made to improve his condition before operation by frequent small feedings, but frequent aspirations of the stomach and loss in weight indicated that the stenosis of the pylorus was almost complete. A blood transfusion was given and a laparotomy performed. An old ulcer was found in the pyloric region. A posterior gastrojejunostomy was done. After the operation the patient quickly gained weight but for several weeks he had a nutritional edema of the feet. On discharge, forty-three days after operation, his weight had increased 35 pounds, to 161 pounds.

*Diagnosis and Summary.*—Duodenal ulcer with pyloric stenosis. Emaciation due to nonutilization of the diet because of vomiting; nutritional edema. Recovery followed a gastrojejunostomy and adequate feeding.

**Case III.**—This man was referred for examination in June, 1935. He was thirty-six years of age, 70 inches tall, and weighed 126 pounds. Complaint was made of marked loss of

weight, exhaustion, ankle edema at night in the past six months, and diarrhea. Symptoms had been present for a year and a half, but he had continued his work as a bank manager. In October, 1933, he gradually lost his appetite and ascribed this to business worries. He vomited at irregular intervals and had occasional diarrhea. In May, 1934, a gastro-intestinal study led to a suspicion of duodenal ulcer; ulcer management gave only temporary relief. In January, 1935, he had from 2 to 6 urgent, watery, explosive stools daily. An Ewald meal showed no free hydrochloric acid, and the administration of hydrochloric acid, cod liver oil and liver capsules caused a temporary gain in weight. The diarrhea, however, continued and on admission to the hospital he had lost the weight previously gained.

Examination showed emaciation, scaphoid abdomen, and slight ankle edema. Blood pressure 100-68. Temperature normal. Teeth and tonsils showed no infection. Thyroid normal; heart and lungs normal; liver and spleen not palpable; no abdominal tenderness. Urine showed a trace of albumin, a few hyaline and occasional cellular casts. Wassermann negative. Blood count normal. Fractional test meal showed normal acid curve. Stools showed only a moderate number of fat globules; they were negative for amebae in fresh smears and in culture; stool cultures showed apparently normal bacterial flora. Proctoscopic examination was negative. Gastro-intestinal x-ray examination was negative save for a peculiar dilatation of the upper small intestine ascribed to atonicity; the colon was uniformly dilated to a moderate degree. Blood calcium 8.8 mg. per 100 cc. Basal metabolic rate — 16.6 per cent.

A balanced diet relatively high in protein content and low in fat was outlined; leafy vegetables and fruits were not restricted. A daily program insuring rest periods was planned. Liver extract was administered intramuscularly twice a week, and liver extract by mouth, calcium gluconate and viosterol were given. Improvement was rapid on this regimen. After four months the intramuscular injections of liver were discontinued. The patient now weighs 165 pounds and feels well. He has one or rarely two formed stools daily. He has had

several mild relapses when he has included much roughage in his diet and had loose stools with an upper respiratory infection.

*Diagnosis.*—Nontropical sprue, relieved by intramuscular injections of liver extract; inanition due to faulty utilization of diet as the result of diarrhea. Noteworthy findings were atonicity of the upper small bowel and the colon, a low basal metabolic rate and a slight hypocalcemia.

**Case IV.**—In this case emaciation was progressive for over ten months; cachexia was present for at least four months prior to death. The patient, a man forty-one years of age, developed painless jaundice after an attack of nausea and vomiting. After eight weeks an exploratory operation was advised and he entered a hospital. There was a delay of three weeks, after which he had a hemorrhage from the bowel. Several blood transfusions were given and finally three months after the onset of the jaundice, an operation was performed. Exploration was brief because of his poor condition. Gallbladder infection, a diffuse hepatitis and inflammation of the pancreas were reported. The gallbladder was drained. Drainage continued for three months, during which time he had 6 attacks of fever and chills. The jaundice finally cleared up and the patient was discharged in an emaciated state but feeling fairly fit. After a month at home he had an attack of vomiting and diarrhea followed by chills and fever. Slight fever continued thereafter.

Finally, about eight months after the initial jaundice, he was admitted to the hospital, cachectic, slightly jaundiced and with slight fever. Red blood corpuscles 3,560,000; hemoglobin 53 per cent. Stools contained bile pigment. A laparotomy had been planned for suspected biliary disease and subacute hepatitis, but the patient's condition scarcely warranted surgery. Signs of gastric retention appeared and a barium meal showed gastrectasis, believed due to duodenal obstruction. A laparotomy was performed but before satisfactory exploration could be carried out the blood pressure fell to a very low level

A jejunostomy was hurriedly done and a catheter implanted, the bowel being fixed to the abdominal wall. Jejunal feedings, averaging 1500 calories daily, were given by means of an automatic pump, and the stomach was aspirated through a nasal catheter. The patient lived for six weeks. Cachexia reached a maximum degree. Terminally, he became deeply jaundiced and developed ascites and edema of the legs. After abdominal paracentesis, a nodular liver was palpable. Necropsy showed a primary carcinoma of the ampulla with extension into the head of the pancreas; the liver was riddled with metastases; the common bile duct and the pancreatic duct were obstructed.

*Diagnosis.*—Carcinoma of the ampulla of Vater, with liver metastases; obstructing jaundice; progressive emaciation of ten months' duration. The prolonged clinical course strikingly emphasizes the fact that food will keep an individual alive indefinitely provided no complications occur. In this case jejunal feedings kept the patient alive for six weeks although emaciation was progressive because of carcinoma which prevented utilization of the nourishment supplied. Death finally occurred after a large percentage of liver tissue had been replaced by metastases.

**Case V.**—This patient, a married woman, twenty-six years of age, was apparently in good health in 1931, when she developed classical symptoms of diabetes. When she came to the hospital for treatment and instruction six weeks later she weighed 120 pounds. Her height was 64 $\frac{3}{4}$  inches. Physical examination was negative; the basal metabolic rate was normal.

Observation has been continued for almost five years. The diabetes has been fairly well controlled by means of insulin and a weighed diet providing 40 to 50 calories per kilogram of her present body weight of 116 pounds. There are, however, marked fluctuations in the fasting blood sugar level and there is occasional glycosuria. Emotional disturbances have been observed to produce hyperglycemia. On the other hand, severe hypoglycemic reactions have occurred after unaccustomed exercise and when meals have been delayed. The susceptibility

to reactions is ascribed to a low hepatic glycogen reserve. Undernutrition has persisted in spite of the provision of calories estimated as sufficient to produce a gain of weight under ordinary circumstances. The undernutrition is believed to be due in part to lack of utilization of the diet because of imperfect control of the diabetes and in part to an associated dysfunction, difficult to classify, of glands of internal secretion other than the pancreas.

*Diagnosis.*—Diabetes mellitus, severe; undernutrition, due in part to imperfect control of the diabetes but chiefly to the type of diabetes present.

**Case VI.**—This patient, a graduate nurse, was admitted to the hospital in 1932 because of weakness, loss of weight, tachycardia, dyspnea on exertion, and nervousness. She was thirty-eight years of age, 67½ inches tall, and weighed 117 pounds. Symptoms had been present for almost four years. In 1928, because of loss of weight, a basal metabolic rate determination was made and found to be +24 per cent. Hospitalization was refused at that time. She gradually lost 32 pounds in weight; her feet and ankles were frequently edematous after walking. Nausea and vomiting had occurred at intervals for a year.

Examination showed marked undernutrition, a small symmetrical goiter, slight exophthalmos, a pulse rate of 100, and a fine tremor of the fingers. A well compensated rheumatic heart lesion (mitral stenosis) was present and had been recognized when she began her hospital training. Basal metabolic rate was +40 per cent. After three weeks of bed rest, a high caloric diet and iodine therapy, her weight increased from 117 to 129 pounds, and the basal metabolic rate dropped from +40 to +17 per cent. A subtotal thyroidectomy was then performed. Sections of the gland showed hyperplastic goiter almost completely involuted by iodine therapy.

Recovery was prompt and complete. She has been able to continue nursing in the past four years. Her present weight is 150 pounds.

*Diagnosis.*—Exophthalmic goiter; inanition due primarily

to hyperthyroidism and secondarily to an inadequate diet; rheumatic heart disease, compensated and nonsymptomatic.

**Case VII.**—This patient, a druggist, thirty-nine years of age, weighs 117 pounds and is 70 inches tall. Fatigue and weakness began three years ago. In the past two years he has lost 35 pounds in weight. Stiffness of the back began two years ago; in the past year he has been unable to bend his spine and he has suffered pain after getting out of bed. For three months he has noted afternoon fever and he has had two or three watery bowel movements daily. There is no history of sweats or hemoptysis.

Examination shows emaciation. The spine is rigid. Thyroid normal. Heart normal save for a rate of 92 to 120. Blood pressure 106-74. The lungs show limited expansion, dullness, high-pitched expirations and râles in both apices. The abdomen is scaphoid, soft. Roentgen examination of the chest shows fibroid changes with cavitation in both apices. Gastro-intestinal x-ray study was negative save for a slight gastric residue eight hours after the barium meal and a colon almost empty after twenty-four hours. Roentgenograms of the spine show spondylitis deformans but no tuberculous caries. The sputum contained many tubercle bacilli; none could be found in the stools examined. The temperature is of septic type with an afternoon rise to 101° and 102° F. White blood corpuscles 19,800.

*Diagnosis.*—Inanition due to active, chronic pulmonary tuberculosis with cavitation; spondylitis deformans.

#### CLASSIFICATION OF INANITION

Brugsch,<sup>1</sup> in 1919, classified emaciation as due to: (1) deficient diet (complete inanition or starvation, and incomplete inanition from food intake, inadequate either as to quantity or quality); (2) increased metabolism, as hyperthyroidism; (3) infection, either acute or chronic; (4) progressive protoplasmic degeneration, as in carcinoma (cachexia); and (5) diseases of metabolism, as diabetes.

It seems evident that the mechanism of emaciation must be

either a deficiency in the intake of food or nonutilization of the diet, or excessive catabolic processes. On this basis, omitting from consideration physiological or constitutional leanness, which rarely produces symptoms, marked undernutrition may be classified as follows:

1. *Inadequate diet:*

- (a) Absolute starvation.
- (b) Undernutrition (semistarvation or incomplete inanition); diet deficient in calories or in essential "protective" constituents (protein, vitamins or minerals), or in both respects.

*Examples:* Habit, early satiety, dietary fads, unbalanced reduction diets, restriction as a result of previous symptoms or treatment; poverty; nervous or psychotic factors (psychogenic anorexia); therapeutic use of semistarvation as in recent treatment of chronic cardiac states.

2. *Faulty utilization of diet:*

- (a) Vomiting, nervous, cardiospasm, pyloric or intestinal stenosis; previous surgical anastomoses.
- (b) Imperfect mastication of food due to absence of teeth.
- (c) Diarrhea, due to sprue, ulcerative colitis, chronic dysentery, etc.
- (d) Absence of free hydrochloric acid; absence of bile in duodenum in jaundice; lack of digestive hormones in pancreatic disease; absence of antianemia substances; deficiency of pancreatic hormone in uncontrolled diabetes; impairment of hepatic function in liver disease.
- (e) Diffuse parenchymatous changes due to bacterial or other toxins; carcinoma.

3. *Excessive catabolism, as in:*

- (a) Hyperthyroidism.
- (b) Hyperparathyroidism.
- (c) Hypophysial cachexia (Simmonds' disease).
- (d) Fevers, acute and chronic.
- (e) Leukemias.
- (f) Malignant tumors.
- (g) Drugs, as desiccated thyroid gland and dinitrophenol.

Obviously, more than one mechanism may be concerned. For example, in fevers and in hyperthyroidism, anorexia may occur and result in a deficient food intake. In dinitrophenol therapy, in addition to increased metabolic activity there may occur dangerous toxic effects on various tissues.

## DISCUSSION

Emaciation, when present, is apparent on inspection of the patient. By comparing the weight with that of the average

for an individual of the same age, height and sex, one may calculate the percentage of underweight. Lesser degrees of undernutrition are frequently disregarded even though the realization is becoming widespread that dietary deficiencies are common and appear to be responsible for a large, varied group of disorders, often ill-defined, including latent scurvy, beriberi, and pellagra; edema; dermatoses; anemia; exhaustion; "gastro-intestinal invalidism" or vague ill-health. Many of these disorders occur despite a fair state of general nutrition and are corrected by insistence upon an adequate supply of the so-called "protective" foods.

An *evaluation of dietary habits* should be a part of every history whether a routine health examination is made or search is made for a pathologic basis of presenting symptoms. Inquiry as to whether the diet contains as a foundation the necessary protective substances (protein, minerals, vitamins) furnished by milk, eggs, leafy vegetables, fruits, meat or other foods of high protein content, and butter, surprisingly often finds a deficiency even in individuals who are apparently well. Since there is ample evidence that prolonged deficiencies may finally lead to severe manifestations, correction is a preventive measure of importance comparable to the correction of obesity after middle age.

In an undernourished individual the history often gives a definite clue as to the probable cause or causes. Many patients admit anorexia and a restricted diet. The symptoms described and the physical findings suggest the special examinations required to detect suspected or possible pathology. When organic disease has been ruled out, and frequently when organic disease is also present, it is necessary to prove and to demonstrate to the patient that his diet is, in fact, inadequate. To demonstrate this the patient must make a list of the items of food that he has actually consumed and the approximate amounts. From such a list one can calculate the approximate calories and reach a conclusion as to the qualitative adequacy of his diet.

The principles of *treatment* of inanition due entirely to a



deficient diet are obvious. The problem is to see to it that the patient actually follows a balanced diet of caloric content in excess of his activity requirements and that he continues on this diet. In practically every case in which uncontrollable systemic disease is absent, a gain in weight is possible provided the patient is cooperative and willing to make the necessary sacrifices. Since there are no practical clinical means of determining the total daily energy output, it is necessary merely to supply a caloric intake that is high and that evidently exceeds the caloric requirements. Execution of this program may, indeed, be difficult. The patient must be taught food values and a program of daily routine, and he must be guided and encouraged. Frequently an adequate diet adjusted to individual idiosyncrasies is prescribed, but one finds that the patient does not eat it. We must ask him to list what he has really eaten. A measured diet or, ideally, a weighed diet is preferable. In hospital management ingestion of the prescribed weighed diet is checked by weighing what is left on the patient's tray.

*Injections of insulin* before meals have been used with good results in many cases of undernutrition. There is, however, a real danger of serious hypoglycemic reactions in emaciated individuals who have little hepatic glycogen reserve. The threat of a reaction may be of definite psychic value in nervous patients who refuse to eat. This is probably the real value of insulin in most instances. Various concentrated preparations of *accessory food factors and minerals* that may be used to supplement the diet are available. Iron, in the form of ferrous sulphate or iron ammonium citrate, is of value since most patients with inanition are anemic; its use frequently causes improvement manifested by increased appetite. The calcium intake, chiefly provided by milk, may be augmented by the use of calcium gluconate, lactate or dicalcium phosphate. Liver extracts are of benefit in many instances and are available for oral or intramuscular use. In addition, vitamin D may be administered in concentrated form (viosterol) or may be furnished with vitamin A in cod liver oil or concentrates, or in

halibut liver oil. Vitamin B may be added by means of various wheat germ concentrates.

In cases of inanition due primarily to causes other than dietary deficiency, recognition of such cases is, of course, essential. Treatment can be successful only in so far as the pathology or dysfunction responsible can be removed, controlled or modified. Thus, mechanical obstruction can be removed; sprue treated with liver extract and diabetes with insulin; and hyperthyroidism decreased by iodine and abolished by thyroidectomy.

In all of these conditions, diet remains of great importance. In patients with nervous vomiting, fluids by any route and feedings by means of a duodenal tube or nasal catheter can be given. In exophthalmic or toxic goiter a high caloric diet enables the patient to gain weight as the hyperthyroidism is checked by iodine therapy, so that the patient approaches operation as a good surgical risk. In emaciation due to tuberculosis the patient's hope of recovery is largely dependent upon his ability to utilize a balanced, high caloric diet that enables him to gain weight, and that provides conditions favorable to healing of the tuberculous process. Even in carcinoma, if the patient can maintain his nutrition, his life can be prolonged until mechanical complications and metastases cause death.

### CONCLUSION

Inanition is a state of extreme undernutrition due to a quantity or quality of nourishment that is deficient for the individual. This deficiency may be due to a manifestly inadequate intake of food or may be relative, due to increased metabolic activity. In other instances the deficiency is due to faulty utilization of an average normal food intake.

Treatment depends on the recognition and relief or modification of any controllable functional or pathological condition that may be present and that prevents normal utilization of foodstuffs or increases metabolic activity. When this has been accomplished, in inanition due to disease as in emaciation due to inadequate diet, continued daily ingestion of a balanced diet

more than sufficient in caloric value to meet the energy requirements of the individual will result in appreciable gain in weight and relief of symptoms due to inanition.

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### THE DIAGNOSIS OF LEUKEMIA IN CHILDHOOD

THE diagnosis of leukemia in infancy or childhood should offer no particular difficulty when one is confronted with a case presenting the classical symptoms and signs of this condition. However, a group of atypical cases, some nonleukemic in nature which have clinically resembled leukemia, and others of a true leukemic nature which have been mistaken for other diseases, often fail to make diagnosis simple and infallible. I wish to present, therefore, a group of cases which have been of interest and offered differential problems in personal experience.

The majority of leukemias in the young are of the acute type.<sup>1</sup> Chronic myeloid leukemia, while of infrequent occurrence, is an accepted and undisputed disease in childhood and the clinical condition is the same as in adult descriptions of the disease. Chronic lymphatic leukemia is said by many never to occur in childhood. There are some well authenticated reports which have recently been collected which make it seem probable that chronic lymphatic leukemia does occur in childhood, though it is certainly the least common type found in young life.<sup>2</sup> In this presentation, therefore, I shall limit myself to a discussion of the acute types of myeloid or lymphatic leukemia.

**Symptoms.**—The symptomatology of leukemia in young life may be very briefly reviewed. The onset is usually acute with fever, headache, loss of appetite, vomiting and asthenia. The initial symptoms are followed by increasing weakness, apathy, pallor, and abdominal or bone or joint pain. Of frequent occurrence are hemorrhages from the mucous membranes

or into the skin, cervical adenopathy, stomatitis, and occasionally nervous symptoms. Dyspnea and cough are noted in cases of mediastinal leukemic tumor. Submaxillary and lacrimal gland swellings are sometimes noted, as well as leukemic skin infiltrations. With the rapid development of anemia the skin becomes white or lemon colored. Leukemic infiltrations occasionally occur in the retina and also in the stomach. Infiltrations are more frequent in the intestinal tract, and, when ulcerative, may cause diarrhea. Metastatic infiltrations may cause tumor formation, as in chloroma.

From these symptoms it may be seen that leukemia may be mistaken for other conditions if a thorough blood examination is not made.<sup>8</sup> Such diseases as diphtheria, ulcerative stomatitis, angina, purpura, scurvy, and endocarditis may be suspected from the initial symptoms manifested in the mouth and throat and from the hemorrhagic tendency and the febrile course.

**Cytologic Differentiation.**—Leukemia may be suspected when leukocytosis or hyperleukocytosis is present, though it may be characterized by leukopenia throughout its course. Morphologic examination of the blood is necessary for a definite diagnosis. Predominance of immature forms of myelocytic or lymphatic type will differentiate myelogenous from lymphatic leukemia. Prevalence of immature cells and smudges aid in the diagnosis.

In mature types of cells the oxydase reaction is positive for the myelocytic type and negative for the lymphocytic type. However, younger myelocytic cells, as myeloblasts, are also oxydase-negative. Cases are reported in which monocytes were the predominant type of cell and these are considered by many to be a third type of leukemia known as monocytic leukemia.<sup>4</sup> These are believed by others to belong to the myeloid or the lymphatic types. *Stem-cell leukemia* is a term applied when very immature cells predominate.

Leukemia is most often associated with a leukocytosis, though it is becoming more generally recognized that many cases are characterized by a leukopenia throughout their course.

I have, therefore, divided the material to be presented into, first, a group where leukocytosis occurs and, second, into a group where leukopenia occurs.

#### GROUP I. DIFFERENTIATION WHEN LEUKOCYTOSIS IS PRESENT

##### (A) Nonleukemic conditions simulating leukemia:

1. Pertussis.
2. Pneumonia.
3. Sepsis.
4. Von Jaksch's pseudoleukemic anemia.
5. Cooley's Mediterranean erythroblastic anemia.
6. Infectious mononucleosis.
7. Mediastinal tumor.
8. Niemann-Pick essential lipoid histiocytosis.

##### (B) Leukemia simulating other conditions:

1. Simulating mediastinal tumor.
2. Simulating rheumatism.
3. Simulating diarrhea.
4. Simulating parotitis.

The following cases illustrate (A) of group I in the classification presented:

**Pertussis** is usually accompanied by leukocytosis and lymphocytosis. Not infrequently hyperleukocytosis of such a degree may be present that a diagnosis of leukemia may be suspected.<sup>5</sup> The following case is illustrative:

**Case I.**—A female infant seven months of age was brought to the hospital because she had had 4 convulsions during the previous night. A history of a cough of two weeks' duration which had gradually increased in severity was obtained. The infant had vomited several times for two days prior to admission; this was attributed by the mother to the coughing. The convulsive seizures had been of a definite clonic nature and were generalized. The infant had been a normal, full term delivery, breast fed, with no history of previous convulsions. The remainder of the history was irrelevant and there was no history of exposure to pertussis.

Physical examination revealed a fat, well-nourished seven-

month-old infant weighing 18 pounds, 14 ounces. The temperature on admission was 100.6° F. There was no cranio-tabes; the anterior fontanel admitted 2 fingertips; there were no enlarged bases and no enlargement of the costochondral junctions and no widening of the epiphyses. Otoscopic examination of the ears revealed pale, normal drums. There was harsh breathing, and a few moist sibilant râles were heard at the left base posteriorly. The breath sounds were vesicular throughout and there was no dulness or impairment of resonance. The heart was not enlarged to percussion, the tones were clear, and there were no murmurs. The abdomen and extremities were normal. The routine complete blood examination showed an amazingly high white blood count. The hemoglobin was 80 per cent (Sahli); red blood cell count 5,025,000; white blood cell count 213,000. The differential count showed polymorphonuclears 27 per cent, small lymphocytes

TABLE 1  
BLOOD FINDINGS IN A CASE OF PERTUSSIS

Day.	White blood count.	Polymorpho-nuclears.	Lymphocytes.		Transi-tional.	Eosino-phil.	Baso-phil.
			Small.	Large.			
First (ad-mission)	213,330	27	5	65	0	3	0
Second	115,600	35	8	56	0	1	0
Third	108,000	38	10	50	1	1	0
Fourth	95,000						
Fifth	88,000						
Sixth	86,500	37	42	18	1	2	0
Eighth	66,000						
Tenth	58,000	24	54	18	1	3	0
Twelfth	24,600						
Fifteenth	21,000	19	66	13	1	1	0

5 per cent, large lymphocytes 65 per cent, and eosinophils 3 per cent. The detailed blood examination is given in Table I.

**Pneumonia** is sometimes accompanied by high initial white blood counts.



**Case II.**—A four-year-old male child was taken sick with fever and slight cough. On initial examination some râles were heard over the right lower chest, and the spleen was palpable. Blood examination showed a white count of over 40,000 with 60 per cent large lymphocytes and mononuclear cells. Two days later the signs of a frank right lower lobular pneumonia were present. Recovery from the pneumonia was uneventful by lysis. There was a gradual drop in the white blood count and the differential count returned to normal on the tenth day.

We may consider the blood reaction in this child as of a lymphatic type. While lymphocytosis is physiologically present in the blood of younger children, still there is a type of child, known as the exudative lymphatic type, who will respond under slight or severe infections with a leukocytosis of lymphatic nature besides showing glandular enlargement and enlargement of the spleen.

Sepsis in infants and young children may show protean manifestations. A leukemia is often simulated when the focus of the infection is obscure, the onset sudden or insidious with fever, the spleen and lymph nodes enlarged, and when a progressively developing anemia with hemorrhagic manifestations and atypical blood findings occur. The correct clinical diagnosis of the following case was not made clear until the microscopic sections made during a careful pathologic study revealed the true nature of the disease.

**Case III.**—A five-year-old male was taken acutely ill with fever and abdominal pain. There was some abdominal muscle spasm. The white blood count showed 22,000 cells, 89 per cent of which were lymphocytes. Appendectomy was followed by pneumonia, following which the white count dropped. Recovery was never complete; the patient developed a stomatitis and febrile periods ensued. The stomatitis cleared and then recurred, accompanied by gingivitis, and an ulcerative lesion of the soft palate developed. Hemorrhages from the mucous membranes of the mouth and purpuric spots of the skin occurred and a dry gangrene of one finger tip was noted. The

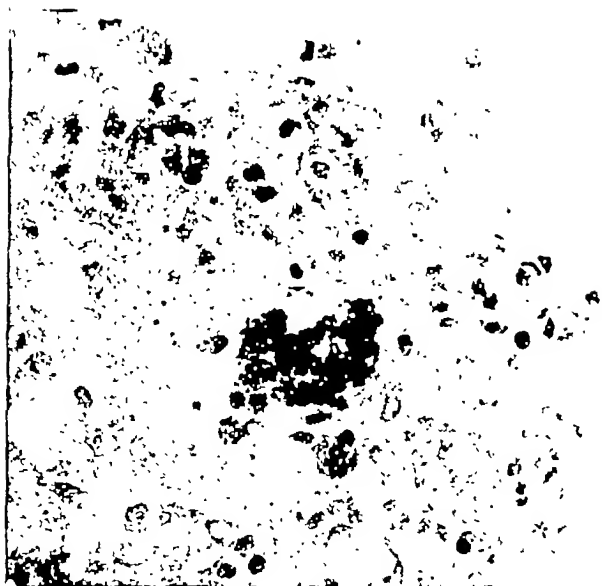


Fig. 1.—Bone marrow from Case III; sepsis simulating leukemia. Showing clumps of cocci. ( $\times 390$ .)

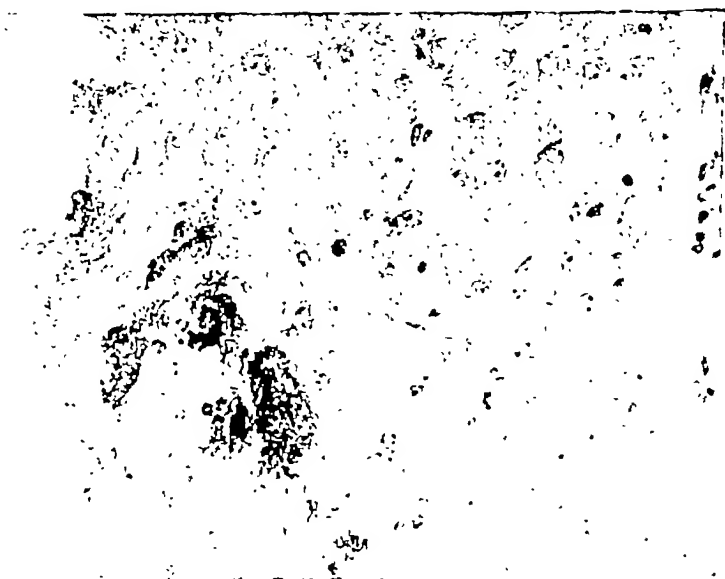


Fig. 2.—Liver from Case III; sepsis simulating leukemia. Showing clumps of cocci. ( $\times 400$ .)

spleen was considerably enlarged and the liver palpable. The white blood count rose to 57,000 and finally dropped to 900. A lymphocytic preponderance was noted practically throughout the course of the disease. Autopsy showed an organizing bronchopneumonia with clumps of cocci disseminated in the bone marrow and liver (Figs. 1, 2). Careful examination of the spleen and lymph nodes revealed no trace of leukemic infiltration (Fig. 3). With the clinical course, signs and symp-

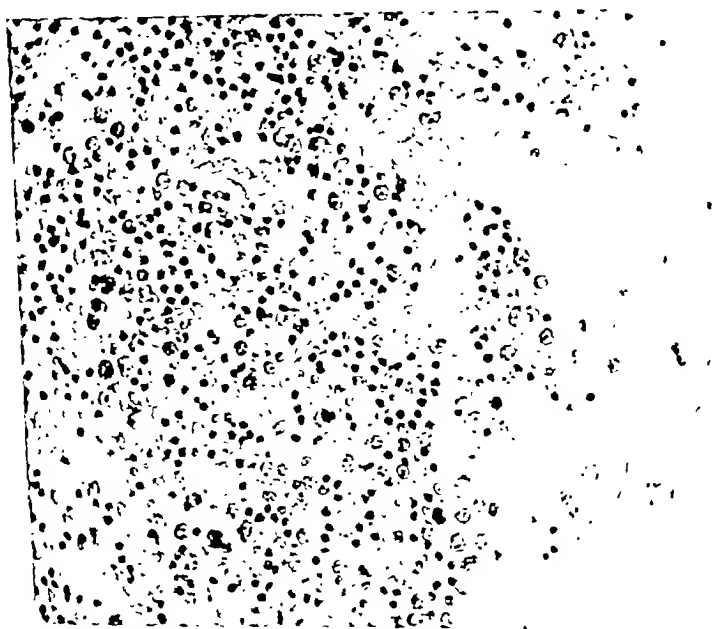


Fig. 3.—Section of lymph node from Case III; sepsis simulating leukemia. Showing no leukemic infiltration. Marked increase in plasma cells, characteristic of sepsis. ( $\times 400$ .)

oms. and the blood examinations, this case would have fitted perfectly into a diagnosis of acute lymphatic leukemia. The complete blood findings are given in Table 2.

Von Jaksch's anemia infantum, pseudoleukemia, occurs in infants from six months to two years of age.<sup>6</sup> It is characterized by a severe anemia, leukocytosis, and with many nucleated red blood cells and other immature cells in the circulating blood. An enlargement of the liver and spleen is

TABLE 2  
BLOOD FINDINGS IN A CASE OF SEPSIS

Date.	Hemo- globin.	Red cells.	White cells.	Neutro- philes.	Lympho- cytes.	Mono- cytes.	Lympho- blasts.
11/14/31	85	4,100,000	22,300	13	87	0	0
11/15/31	80	3,700,000	14,300	28	70	2	0
11/17/31	80	3,600,000	6,500	27	73	0	0
11/21/31	75	3,700,000	9,250	19	81	0	0
11/25/31	75	3,800,000	18,500	15	81	4	0
1/11/32	65	3,200,000	37,050	8	92	0	0
3/21/32	30	2,000,000	14,300	9	91	0	0
4/ 4/32	30	1,500,000	57,600	3	93	0	4
4/14/32	45	2,600,000	33,600	28	70	2	0
4/18/32	45	2,200,000	13,000	1	99	0	0
4/25/32	41	1,900,000	3,300	9	91	0	0
5/ 4/32	30	1,500,000	900	12	88	0	0

also present. The condition has been associated with rickets and infection, and is probably a severe form of secondary anemia due to the association of these two conditions.

**Case IV.**—The following case illustrates this condition. A thirty-month-old female infant was seen with the complaints

TABLE 3  
BLOOD FINDINGS IN A CASE OF JAKSCH'S ANEMIA

Date.	Hemo- globin.	Red cells.	White cells.	Neutro- philes	Lympho- cytes.	Mono- cytes.	Myelo- cytes.	Normo- blasts per 100 white blood cells
2/1	35	2,070,000	38,800	53	35	2	10	40
2/12	25	2,050,000	40,200	53	33	3	11	30
2/17	30	2,080,000	34,600	55	30	4	11	55

of vomiting, constipation, loss of weight, and pallor of one month duration. Examination revealed a pale, poorly nourished infant with a rachitic rosary and widening of the epiph-

yses. The liver and spleen were large. The temperature was of a subfebrile character and the Wassermann reaction was negative. The blood findings showed a leukocytosis with an increase in nucleated red blood cells, and a detailed examination of the blood is given in Table 3.

**Erythroblastic anemia** is a rare form of anemia first described and named by Cooley,<sup>7</sup> who differentiated it from Von Jaksch's anemia. It occurs in infants of families originating in Mediterranean countries and is of congenital, familial and racial incidence. It is a slowly progressing anemia characterized by large numbers of nucleated red cells in the peripheral blood. There is enlargement of the liver and spleen, a mongoloid facies, and a characteristic change in the bones on x-ray which show a thinning of the cortices and a widening of the medullary portion with prominent trabeculation and radiating spicules from the inner table of the skull.

**Case V.**—A Greek male infant, two and one-half years old, had been normal at birth. At eight months of age it was

TABLE 4  
BLOOD FINDINGS IN A CASE OF COOLEY'S ERYTHROBLASTIC ANEMIA

Date.	Hemo- globin.	Red cells.	White cells.	Neutro- philes.	Lympho- cytes.	Mono- cytes.	Myelo- cytes.	Normo- blasts per 100 white blood cells.
10/25	35	2,020,000	18,200	49	41	1	9	5
10/28	35	1,960,000	26,000	54	39	1	6	7
11/1	30	2,700,000	15,200	64	32	1	3	3
11/3	35	2,600,000	21,600	62	26	3	9	4
11/9	25	1,400,000	16,800	47	40	3	10	2
11/14	30	1,800,000	31,900	58	37	2	3	3
11/16	25	1,140,000	21,500	52	38	9	1	1
11/25	35	2,120,000	26,400	64	27	6	4	0
11/30	30	1,760,000	20,000	49	48	0	3	1
12/8	25	1,100,000	10,200	55	43	0	2	0

noted that his abdomen became prominent. On examination he showed a marked pallor, his temperature was subfebrile

with an occasional sudden rise; his expression was dull with a wide flat nose and with his prominent abdomen he gave a somewhat mongoloid appearance. His liver was enlarged and his spleen extended nearly to the umbilicus. A detailed blood picture is given in Table 4.

**Acute infectious mononucleosis**, sometimes termed Pfeiffer's disease or glandular fever, is an acute illness with general glandular swelling, enlargement of the spleen and fever of long or short duration.<sup>8</sup> There is usually a reddening of the throat and at times follicular spots or a pseudomembranous type of angina are present. A leukocytosis is present and is manifested by an increased number of small and large lymphocytes and monocytes. The course of the disease is usually mild. Thoracic and abdominal symptoms may occur from enlargement of the lymph glands in these regions.

The resemblance at the onset to acute leukemia may be striking with the throat lesions, fever, glandular and splenic enlargement. However, the throat lesions are less extensive than in leukemia and clear up rapidly, the disease is generally less severe, and the anemia and hemorrhagic symptoms characteristic of leukemia are absent. Diagnosis from the blood picture alone is not always possible, though some authors maintain that the large lymphocytes and monocytes found in infectious mononucleosis are pathognomonic for this condition.

A diagnostic test for infectious mononucleosis has recently been reported. It has been found that heterophile antibodies demonstrable in the form of sheep-cell agglutinins have been recorded in high concentration in infectious mononucleosis. The existence of heterophile antibodies was first recognized by Forssman<sup>9</sup> and they have been investigated by numerous observers, particularly by Davidsohn<sup>10</sup> in recent times. It has been found that certain substances, such as emulsions of cells from the organs of various mammals, birds and fish, when injected into animals such as the rabbit, give rise not only to specific antibodies but also to nonspecific antibodies which may be demonstrated in the form of hemolysis and agglutinins for sheep cells. Davidsohn observed the presence of hetero-

phile antibodies in serum disease. Paul and Bunnell<sup>11</sup> were the first to show that heterophile antibodies in the form of sheep cell agglutinins were present in the serum of a patient suffering with infectious mononucleosis. They found that the antibodies were present in a much higher concentration in this condition than in the blood from serum disease or other conditions. Other investigators have since shown that this test for heterophile agglutinins for sheep cells is a valuable diagnostic procedure in differentiating infectious mononucleosis from other clinical conditions of a similar nature. Agglutination has occurred when the titer of the serum has ranged from 1:64 to 1:4096 in cases of infectious mononucleosis.<sup>12</sup> In serum disease the agglutination has been positive in dilutions as high as 1:64. In other conditions the highest titer for agglutination has been 1:8. It can, therefore, be said that cases presenting the clinical signs and symptoms of this disease with the accompanying blood picture whose blood serum shows an agglutination for sheep cells in a dilution of at least 1:64 can be diagnosed as infectious mononucleosis.

**Case VI.**—A four-and-one-half-year-old female child was taken acutely ill with fever, sore throat, vomiting and enlarged

TABLE 5  
BLOOD FINDINGS IN A CASE OF INFECTIOUS MONONUCLEOSIS

Date.	Hemo- globin.	Red cells.	White cells.	Neutro- philes.	Lympho- cytes.	Mono- cytes.	Remarks.
9/25	75	4,500,000	28,000	50	48	2	Spleen 2+
10/4	75	4,400,000	14,600	42	50	8	Spleen 1+
10/10	79	4,500,000	22,500	26	60	14	Spleen 1+
10/20		....	22,100	38	60	2	Spleen 1+
10/28	75	4,400,000	23,300	32	60	8	Spleen tip
11/20	78	4,800,000	30,100	24	66	10	Spleen 0
12/15	78	4,800,000	17,500	36	54	10	

cervical glands. The spleen was palpable 2 fingerbreadths below the costal margin. The acute illness was of four days' duration and the spleen was somewhat smaller after one week

and remained palpable for six weeks after the onset. The blood was marked by a leukocytosis with increase in the lymphocytes and mononuclear cells which were persistent for some time. There were no hemorrhages or petechial spots on the skin. The detailed blood examination is given in Table 5.

**Essential lipid histiocytosis (Niemann-Pick disease)** is a disease which occurs in infants under two years of age and is marked by mental and physical retardation, an early enlargement of the abdomen and enormous enlargement of liver and spleen.<sup>13</sup> Irregular fever occurs during the course of the disease. The blood findings are marked by slight to moderate anemia, leukocytosis with some increase in the mononuclear cells. Vacuolization of the lymphocytes and monocytes has been noted.

**Case VII.**—A female infant aged eight months complained of anorexia, irritability and protuberant abdomen for two months. The infant was pale and irritable, with a suggestive mongoloid appearance and gave signs of mental retardation.

TABLE 6  
BLOOD FINDINGS IN A CASE OF NIEMANN-PICK DISEASE

Age, months.	Hemo- globin.	Red cells.	White cells.	Neutro- philes.	Lympho- cytes.	Mono- cytes.	Others.
8	55	3,400,000	14,200	45	55	..	Vacuolation of lymphocytes and monocytes.
9	63	3,450,000	15,000	35	65	..	
10	60	3,840,000	13,250	31	65	4	
12	60	3,830,000	15,700	31	60	9	
13	62	3,600,000	7,000	45	50	5	
15	80	4,310,000	14,500	54	44	2	
Postoperative	65	3,800,000	14,800	49	48	3	

The liver and spleen were greatly enlarged. The eyegrounds were normal and the serologic examination was negative. A splenectomy was performed and the typical foam cells were found in the spleen.

The detailed blood examination is given in Table 6.



The following cases illustrate (*B*) of Group I:

**Mediastinal enlargements** of the thymic area occur in leukemia.<sup>14</sup> This condition may be present before actual blood changes have occurred, and the symptoms from pressure on the trachea may cause dyspnea. Irradiation of the thorax will give relief in those cases where leukemic blood changes have not already occurred and the mass may completely recede, as shown by x-ray examinations. However, the condition is only temporary, as a leukemic blood picture and signs of a true leukemia develop after an interval.

**Case VIII.**—The case of a ten-year-old boy with a non-leukemic round-cell tumor of the mediastinum with a leukocytosis of 40,000 simulated this condition. The complaints were cough and a 7-pound loss of weight, shortness of breath, dyspnea and pain in the side present for one month. There was an inconstant fever, and the boy was thin and pale, showed immobility of the left chest, flatness over the left lung anteriorly and dulness posteriorly. Thoracentesis resulted in a dry tap. A laryngeal cough developed and death occurred suddenly.

TABLE 7  
BLOOD FINDINGS IN A CASE OF MEDIASTINAL TUMOR

Date	Hemoglobin	Red cells.	White cells.	Neutrophiles	Lymphocytes	Monocytes
5/13	75	4,160,000	15,000	46	44	10
6/7	65	3,800,000	40,000	52	40	8

Autopsy showed an infiltrative round-cell tumor of the anterior mediastinum invading the lung and pericardium. The blood findings are given in Table 7.

**Arthritis** may be associated with leukemia, with pains and swellings of the joints.<sup>15</sup> When the blood count is low, an acute rheumatic fever may be erroneously thought of.

**Case IX.**—A male, nine years of age, complained of swelling of the right elbow associated with fever. The child was

pale, thin and in considerable pain upon flexing his right arm. There was a considerable swelling of the right elbow, a general glandular enlargement, most marked in the cervical region; a palpable liver and an enlarged spleen. The temperature was 104° F. The white blood count was 10,450. The course of the disease was febrile; an increasing leukocytosis developed; swelling and redness of the left elbow occurred as well as of the metacarpals of the left hand. Finally the white blood count exceeded 40,000 and petechiae and hemorrhages occurred. Autopsy revealed the typical picture of an acute lymphatic leukemia.

The detailed blood findings are given in Table 8.

TABLE 8

BLOOD FINDINGS IN A CASE OF LEUKEMIA SIMULATING RHEUMATISM

Date.	Hemo- globin.	Red cells.	White cells.	Neutro- philes.	Lympho- cytes.	Myelo- cytes.	Lympho- blasts.
4/15	60	3,200,000	10,450	4	93	1	2
4/19	55	3,600,000	8,100	1	95	0	4
4/30	55	3,900,000	15,300	4	86	0	10
5/8	60	3,500,000	23,300	10	80	10	0
5/10	60	3,200,000	44,800	17	60	8	15
5/20	60	3,100,000	148,000	8	79	3	10
5/26	55	3,000,000	340,000	2	98	0	0
5/30	..	.....	104,000	6	94	0	0
6/2	45	2,000,000	96,500	10	80	0	10
6/5	40	2,400,000	94,000	0	91	0	9

Salivary gland enlargement may be associated with lymphatic leukemia. Mikulicz described a condition of chronic enlargement of the salivary and lacrimal glands, which was bilateral and painless, and which he believed due to a low grade infection. Cases of this type are known as Mikulicz's disease while those associated with other conditions have been termed Mikulicz's syndrome.<sup>10</sup> The relationship of mumps, syphilis and tuberculosis to this disease has been suggested.

**Case X.**—A nineteen-month-old infant was admitted with the complaint of bilateral swelling of the face for one month. He was well-nourished, slightly pale, with bilateral swelling of the submaxillary, parotid and lacrimal glands (Fig. 4). There was a general glandular enlargement. The white count on admission was 11,200, and this showed a decrease with a later



Fig. 4.—Nineteen-month-old infant with acute lymphatic leukemia, Case X. Showing swelling of submaxillary, parotid, and lacrimal glands, as well as enlargement of liver and spleen. Mikulicz's syndrome.

rise and terminal fall. The spleen was at first slightly palpable and later became greatly enlarged. During the last week of the disease the spleen rapidly shrank until it was barely palpable and the facial swellings receded. At autopsy the typical findings of acute lymphatic leukemia were demonstrated.

The detailed blood findings are given in Table 9.

TABLE 9

BLOOD FINDINGS IN A CASE OF LEUKEMIA SIMULATING MIKULICZ'S DISEASE

Date.	Hemo- globin.	Red cells.	White cells.	Neutro- philes.	Lympho- cytes.	Mono- cytes.	Myelo- cytes.
5/15	60	3,300,000	11,200	16	72	8	4
5/21	50	3,100,000	14,200	6	90	4	0
5/29	60	3,000,000	2,400	20	80	0	0
6/6	55	2,750,000	5,300	50	42	3	5
6/9	50	3,300,000	3,720	64	31	5	0
7/10	65	3,700,000	2,500	51	38	3	8
7/16	65	4,600,000	7,850	24	72	2	2
7/19	.	.....	12,600	13	73	5	9
7/29	45	2,600,000	24,550	1	92	5	2
7/31	40	2,200,000	6,350	1	96	3	0
8/4	35	1,500,000	2,000	0	98	2	0
8/7	..	.....	1,550	0	100	0	0

The conditions above described were associated with *leukocytosis*. The following conditions are associated with *leukopenia*.

## GROUP II. DIFFERENTIATION WHEN LEUKOPENIA IS PRESENT

## (A) Nonleukemic conditions simulating leukemia:

1. Sepsis.
2. Agranulocytosis.
3. Gaucher's disease.
4. Nonlipoid splenohepatomegaly; Letterer-Siwe's disease.
5. Aplastic anemia.
6. Malaria.

## (B) Aleukemic leukemia simulating other conditions:

1. Simulating sepsis.
2. Simulating appendicitis.
3. Simulating aplastic anemia.

The following cases illustrate (A) of Group II in the classification.

**Sepsis** in infants and children may be marked by leukopenia, often of a severe degree. The disease may be manifested by hemorrhages, petechiae and enlargements of liver and spleen, and closely simulating leukemia.<sup>17</sup>

**Case XI.**—A female infant, nine months of age, presented the complaints of anemia and purpuric spots on the skin for six weeks. The infant was acutely ill, with marked pallor and a distended abdomen. The liver and spleen were both considerably enlarged. The blood findings showed a progressive anemia with leukopenia and a relative lymphocytosis. They are given in detail in Table 10.

TABLE 10  
BLOOD FINDINGS IN A CASE OF SEPSIS WITH LEUKOPENIA

Date.	Hemo- globin.	Red cells.	White cells.	Neutro- philes.	Lympho- cytes.	Undiffer- entiated mono- cytes.	Others
2/16	52	2,800,000	20,600	43	57	0	0
2/20	53	2,600,000	8,600	56	31	1	12 myelo- cytes.
3/10	40	1,900,000	4,000	0	70	30	0
3/15	30	900,000	3,600	0	65	35	0

**Agranulocytic angina**, or malignant neutropenia, is not so common in children as in adults<sup>18</sup>. The disease is characterized by an ulcerative nasopharyngitis, leukopenia and reduction or absence of granulocytes. Lymphocytes and monocytes are unchanged. The fundamental pathology occurs in the bone marrow. Causes of neutropenia are (1) shifting of neutrophils from the peripheral blood; (2) normal bone marrow, excessive destruction of neutrophils; (3) exhaustion or inability of bone marrow to produce neutrophils. The bone marrow is hyperplastic and microscopically shows decrease in activity of myelocytic cells. Many authors question the entity of this disease as described by Schultze, and prefer to consider the symptoms a syndrome which is capable of being produced by various etiologic agents.

**Gaucher's disease** is characterized by an insidious onset with the gradual enlargement of the spleen and later of the liver. Leukopenia is the characteristic blood finding with little change in the differential count. Hemorrhagic diathesis is

absent, and the course is protracted. Splenic puncture reveals typical Gaucher cells, pathognomonic for the disease.

**Letterer-Siwe's Disease. Nonlipoid Splenohepatomegaly, so-called "Reticulo-endotheliosis."**—I recently have encountered a very interesting case belonging to this group, which was mistaken clinically for aleukemic lymphatic leukemia.<sup>19a</sup>

This condition is characterized by a marked splenomegaly with moderate to considerable enlargement of the liver, a hemorrhagic tendency chiefly manifested as purpura, an involvement of the osseous system which may be manifested by tumor formation, or only may be recognized with the aid of the x-ray or, pathologically, a general enlargement of the lymph glands, and a blood picture which is characterized by a severe secondary anemia and slight leukocytosis to leukopenia.

The pathologic changes are characterized by a generalized hyperplasia and proliferation of the cells of the reticulo-endothelial system in various organs. The characteristic cells are large mononuclear cells, round or polygonal in shape, containing a nucleus poor in chromatin and a pale staining cytoplasm.

Splenic puncture may reveal an increased number of these typical pale staining cells of a nonlipoid nature so that a correct clinical diagnosis may be made. The course of the disease is gradually downhill, accompanied by fever of a continuous nature. The duration of the disease has varied from a few weeks to several years.

**Aplastic anemia** is a progressive anemia associated with splenomegaly, leukopenia and granulopenia and marked by a diminution of the granulocytic elements in the differential picture and a lack of regeneration of the red blood cells. The characteristic pathologic finding is a fatty or fibrous replacement of the bone marrow. The disease is probably a symptom-complex and may be caused by numerous etiologic factors. The condition can only be positively diagnosed by a pathologic examination of the bone marrow.

**Malaria**, while not often seen in temperate zones, may be confused with leukemia in regions where it is prevalent.<sup>19b</sup>

The splenomegaly with leukopenia may be mistaken for an aleukemic leukemia. There are cases reported in which malaria has complicated a leukemia. In chronic malaria the monocytes are often increased and occasionally a myelocytic increase may be noted. Where it is possible to demonstrate the malarial parasites in the blood the differential diagnosis should not be difficult.

The following cases illustrate (*B*) of Group II:

**Aleukemic leukemia** and sepsis with leukopenia are at times extremely difficult to differentiate. The following case is illustrative and proved at autopsy to be one of aleukemic lymphatic leukemia.

**Case XII.**—A seven-year-old female child complained of fever, vomiting, nose bleed and pallor of two weeks' duration.

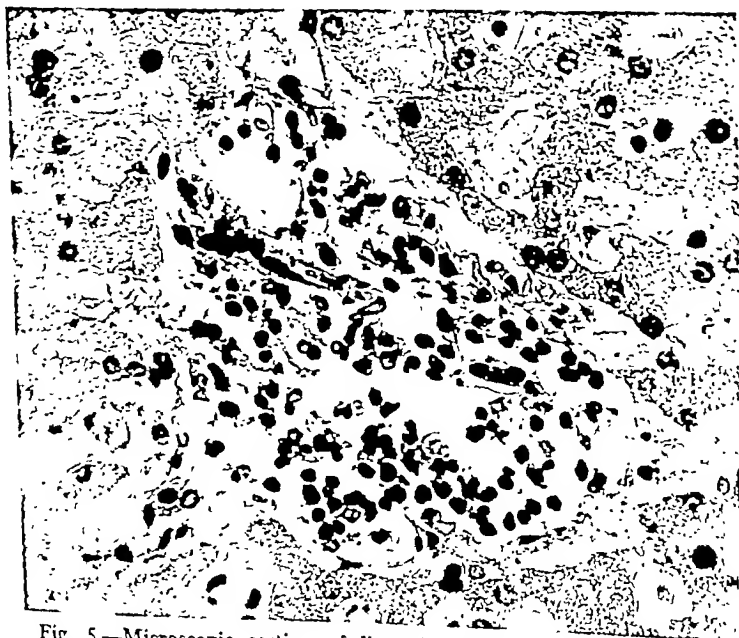


Fig. 5—Microscopic section of liver from case of aleukemic lymphatic leukemia simulating sepsis. Case XII. Showing periportal leukemic infiltration of liver. ( $\times 650$ )

On admission the temperature was  $103^{\circ}$  F., there was some bleeding from the nose, and the spleen was slightly enlarged.

There was a marked anemia with leukopenia. Hemolytic streptococci were cultured from the blood. A diagnosis of sepsis was made and 5 transfusions were given at intervals. After six weeks the hemoglobin and red count were within normal values and the white count 7400. The child was afebrile and was discharged in excellent condition. Two weeks later she returned with a marked anemia and petechiae on the extremities. There was 32,800 white cells, of which 96 per

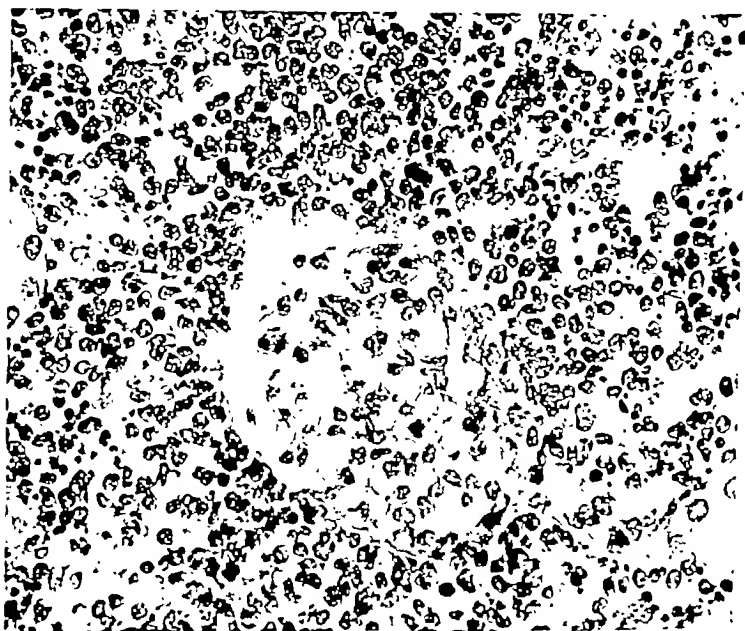


Fig. 6.—Microscopic section of kidney from case of aleukemic lymphatic leukemia simulating sepsis. Case XII. Showing leukemic infiltration. ( $\times 600$ .)

cent were lymphocytes. A septic course marked by angina and hemorrhages ended in death. The autopsy revealed the characteristic findings of lymphatic leukemia (Figs. 5, 6).

The detailed blood examinations are given in Table 11.

**Aleukemic leukemia** may simulate *appendicitis*. It will be noted that in a previous case here reported a child was operated for appendicitis and developed a sepsis simulating leukemia until autopsy proved the true condition.



TABLE 11

BLOOD FINDINGS IN A CASE OF ALEUKEMIC LEUKEMIA SIMULATING SEPSIS

Date.	Hemo- globin.	Red cells.	White cells.	Neutro- philes.	Lympho- cytes.	Mono- cytes.	Immature lympho- cytes.
10/23	30	1,060,000	2,125	24	75	6	1
			Five blood transfusions				
12/7	65	4,100,000	7,400	38	57	5	6
12/24	40	1,900,000	32,800	2	96	2	6
12/27	35	1,500,000	5,600	9	89	2	6
12/31	40	2,000,000	14,000	20	75	5	6
1/3	..	..	9,500	15	80	5	6
1/7	30	1,500,000	2,700	5	93	2	6

Case XIII.—A male child, six years of age, developed a sudden night attack of pain in the lower abdomen, tenderness and rigidity in the lower right quadrant with a white blood count of 6000. The appendix was removed and revealed little evidence of inflammation. A similar attack occurred three weeks after operation and attacks of pain with fever occurred at intervals. Numerous transfusions were given, the leu-

TABLE 12

BLOOD FINDINGS IN A CASE OF ALEUKEMIC LEUKEMIA SIMULATING APPENDICITIS

Date.	Hemo- globin.	Red cells.	White cells.	Neutro- philes.	Lympho- cytes.	Mono- cytes.	Immature lympho- cytes.
8 '11	40	3,800,000	3500	40	60	0	0
8 '18	50	2,600,000	2100	20	66	2	12
9/1	58	3,600,000	5400	10	87	1	2
9/25	40	2,250,000	6200	8	80	3	9
10/1	42	2,900,000	5300	9	80	4	7
10 17	46	2,800,000	5000	4	88	2	6

kocytes dropped and pentnucleotide was administered. There was a septic course with gradual decline. Liver and spleen were never palpable. At autopsy the diagnosis of lymphatic leukemia was established. The detailed blood examination is given in Table 12.

Aleukemic leukemia may simulate aplastic anemia and, as has been said, the diagnosis can only be definitely established by a pathologic examination of the bone marrow.<sup>20</sup>

The following unusual case which was under close observation for over two years showed an almost constant leukopenia accompanied by splenomegaly, anemia and lymphocytosis. The prolonged course and associated blood findings with neutropenia and the findings of myelocytes on only 2 occasions made a clinical diagnosis of aplastic anemia seem probable.

**Case XIV.**—A female child was first admitted at the age of four years with the complaints of weakness, loss of weight and night-sweats. The child was thin and pale with enlarged abdomen; anemia was marked. The liver and spleen were palpable. There were a few purpuric spots on the skin. Over a two-year period there were repeated exacerbations of fever, hemorrhages and enlargements of liver and spleen. During periods the symptoms subsided and the anemic condition improved. There were occasional complaints of pain over the long bones. Numerous transfusions were given during the course of the disease. Two months before the fatal termination blindness developed in the left eye. At times during the course of the disease the liver and spleen were barely palpable, while at other periods the enlargement reached to the umbilicus. Autopsy showed typical leukemic infiltrations of myeloid cells and the final diagnosis was chronic aleukemic myeloid leukemia. The detailed blood findings are given in Table 13.

**Leukemia in the Newborn Period.**—Leukemia may occur at a very early age. V. Kornmann<sup>21</sup> describes its occurrence in the newborn period in a six weeks' old female infant. Autopsy demonstrated that the case was one of acute myeloid leukemia of the myeloblastic type. In 1922 Koch<sup>22</sup> described this disease in 2 newborn infants. In 1924 Stransky<sup>23</sup> described myeloid leukemia in a three weeks' old female infant. In the same year Opitz<sup>24</sup> described the disease in a twelve weeks' old infant. Büngeler<sup>25</sup> in 1931 described congenital myeloid leukemia in a stillborn child. These 6 reports

TABLE 13

BLOOD FINDINGS IN A CASE OF ALEUKEMIC LEUKEMIA SIMULATING ATLANTIC

Date.	Hemo- globin.	Red cells.	White cells.	Neutro- philes.	Lympho- cytes.	Monoc- ytes.	Myelo- cytes.	Im- mature leuko- cytes
6/11/31	50	2,100,000	2200	13	86	0	1	0
6/25	65	2,300,000	3750	16	84	0	0	0
7/8	55	3,200,000	4300	11	86	3	0	0
7/22	65	3,400,000	3600	16	84	0	0	0
8/4	55	3,100,000	3250	36	61	3	0	0
9/18	60	3,800,000	4200	5	76	19	0	0
10/4	60	3,900,000	5900	26	62	10	0	2
10/25	55	2,600,000	4900	26	64	4	0	0
11/13	55	2,900,000	5000	32	62	5	0	1
11/30	75	4,500,000	5500	40	53	7	0	0
12/31	75	5,100,000	5900	22	70	8	0	0
2/ 4/32	70	3,000,000	2800	10	88	1	0	1
4/6	45	2,500,000	1700	1	84	8	0	7
5/26	70	4,100,000	4800	14	65	3	0	15
7/ 1	30	1,200,000	1400	2	92	6	0	0
8/ 9	40	1,300,000	1600	16	84	0	0	6
10/31	70	4,400,000	7900	16	74	4	0	0
11/27	..	3,600,000	3200	9	61	10	0	20
12/ 9	20	900,000	3800	15	78	3	4	0

substantiate the occurrence of leukemia in the newborn period of life. Büngeler's case is of special interest as it occurred in a stillborn infant of seven months' gestation measuring 38 cm. in length and weighing 1620 Gm. Smears from blood of the vena cava and heart revealed 80 per cent myeloblasts and myelocytes. Many of these cells gave a positive oxydase reaction. There were many myeloid cells noted in the liver, spleen, myocardium, lungs, kidneys, and other organs. We may, therefore, be permitted to speak of a congenital type of leukemia. Baar and Stransky<sup>28</sup> quote several cases of congenital or newborn leukemia from the older literature and state that the existence of this condition has been proved beyond doubt. They further cite cases in which leukemic mothers have given birth to normal children. From the cases which

they cite they conclude that acute or chronic leukemia is not transmitted from mother to child.

There are several conditions occurring in the newborn which may be mistaken for leukemia. Under the term erythroblastosis of the newborn is now included the condition formerly known as icterus gravis neonatorum.<sup>27</sup> Newborn infants suffering from this condition either at birth or a few hours thereafter develop a rapidly deepening jaundice which is asso-

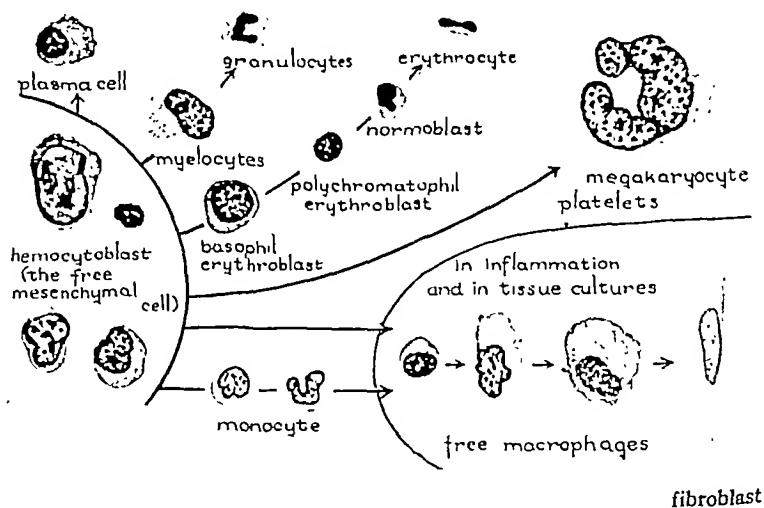


Fig. 7.—Schematic representation showing the potentialities for the development of granulocytes, normoblasts, macrophages and fibroblasts from hematocytoblasts and lymphocytes. (Maximow and Bloom's Textbook of Histology.)

ciated with anemia and a great number of immature erythrocytes in the circulating blood. Associated with the jaundice, anemia and erythroblastic blood picture are familial history, slight edema, extensive extramedullary hematopoietic foci in the liver and various organs with increased iron deposition and occasionally a nuclear icterus in the brain. The blood picture is characterized by a severe hyperchromic anemia with great numbers of immature red blood cells and occasional young white cell forms. Poikilocytosis, polychromatophilia with

stippling and increase in reticulated blood cells are noted. The icterus index is markedly increased and a biphasic van den Bergh reaction is present.

It might be easy in examination of the blood smear from such a case to mistake the nucleated red blood cells, some of which are present in a very early form, for leukocytes. Several investigators, in fact, have termed this condition fetal erythro-leukoblastosis and likened it to leukemia.<sup>25</sup> However, careful



Fig 8—Tissue culture from normal blood, showing development of macrophages and fibroblasts. (After Maximow, 1928.)

study of the pathologic histology has convincingly showed that erythroblastosis of the newborn is not related to leukemia. From present knowledge the cause of erythroblastosis of the newborn can best be ascribed to an embryonal persistence of hematopoiesis of erythrocytes in various organs.

Congenital syphilis may manifest itself by fever, purpura, enlargement of the liver and spleen, with anemia and occasionally with the presence of a great number of normoblasts

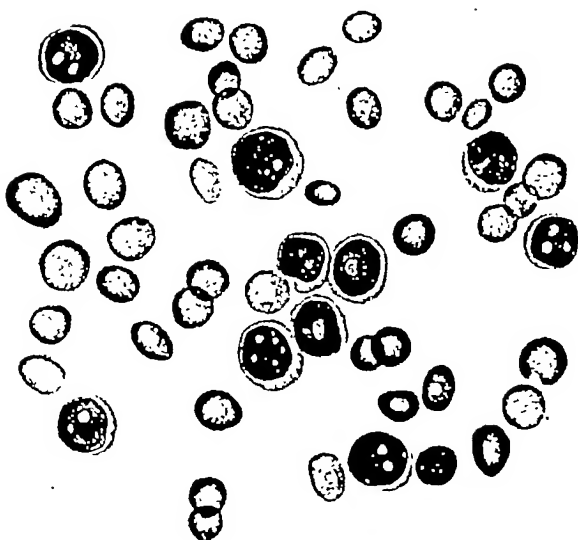


Fig. 9.—A stained smear from peripheral blood of a case of stem-cell leukemia.  
(After Timofejewsky and Benewolenskaja.)

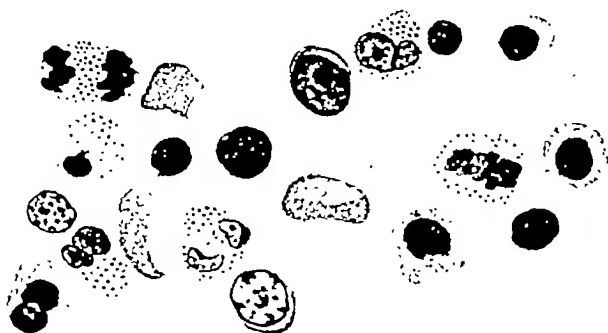


Fig. 10.—Tissue culture from blood of patient shown in Fig. 9, showing growth of granulocytes and normoblasts. The stem cells from the original blood may now be identified as myeloblasts. (After Timofejewsky and Benewolenskaja.)

and a few immature myeloid cells in the blood stream.<sup>20</sup> If the typical luetic manifestations which accompany these phys-

ical and hematologic findings are recognized, the differentiation from leukemia should not be difficult.

**Tissue Culture of Blood.**—Since 1914 when it was first attempted, tissue cultures of leukemic blood have been made in attempts to differentiate and establish the origin of the cell types involved in the leukemias.<sup>30</sup>

In cultures of normal blood it has been found that macrophages and fibroblasts develop from lymphocytes and monocytes (Figs. 7, 8). In cultures of lymphatic leukemia the lymphocytes again develop into macrophages and fibroblasts.

On the other hand, in cultures of blood from myeloid leukemia the myeloblasts develop not only into macrophages and fibroblasts but also into myelocytes, granulocytes and normoblasts.<sup>31</sup> It is thus possible that by tissue culture we may be able to separate lymphoblasts from myeloblasts in cases of stem-cell leukemia where differentiation is otherwise impossible (Figs. 9, 10).

The following report may illustrate the value of tissue culture of the blood in determining the type of leukemia.

**Case XV.**—E. S., a thirteen-year-old girl, was taken ill with fever, epistaxis, bleeding from the gums, and purpura. Her spleen and liver were enlarged and there was general glandular enlargement. The child was acutely ill. Peripheral blood examination is given in Table 14.

TABLE 14

Date	Hemoglobin.	Red cells.	White cells.	Lymphocytes.		Oxydase reaction.
				Small.	Large.	
11 19	55	2,464,000	55,400	14	86	Entirely negative.
11 27			155,000	All lymphocytes.		Entirely negative.

Morphologically, we believed that we were dealing with an acute lymphatic leukemia. However, tissue cultures of the blood from this patient, at eighteen hours, contained at least 65 per cent myelocytes. We, therefore, had determined that

the cells in the peripheral blood which we took to be all lymphocytes and which were oxydase-negative, were in reality cells of the myeloid series, probably oxydase-negative myeloblasts. Instead of an acute lymphatic leukemia the case was really one of acute myeloblastic leukemia.

### CONCLUSIONS

A group of nonleukemic and leukemic cases are here discussed and illustrative examples presented to show how atypical cases of leukemia may be confused with nonleukemic conditions including those with leukocytosis and those with leukopenia. Cytologic as well as blood tissue culture methods of differentiation are briefly discussed. In some of these atypical cases clinical differentiation may be impossible. Sometimes even after the most careful pathologic review, the exact nature of the case may remain in doubt.

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## CLINIC OF DR. HARRY L. HUBER

### UNIVERSITY OF CHICAGO MEDICAL CLINICS

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#### FOOD ALLERGY

WHILE the old saying "what is one man's food is another man's poison" was trite long before the words "food allergy" were used, the clinical significance of the widespread sensitization to foods was not adequately recognized until allergists had demonstrated that in many cases of asthma and eczema (dermatitis) the symptoms were caused by commonly used foods. In the twenty-five years that have elapsed since the beginning of this work it has been shown repeatedly that a sensitization to a food or foods is the cause of symptoms in many cases of not only asthma and eczema, but also in many cases of urticaria (hives), migraine, and vasomotor rhinitis, and in some cases of arthritis, acne, epilepsy, certain gastro-intestinal disorders, agranulocytic angina, and intermittent hydrarthrosis. The relationship of food allergy to other types of clinical disorders is being studied and, without doubt, some of these will be added to the above list. The line of demarcation is as yet not clearly defined.

In the early days of this work tests were made with only a few of the most commonly used foods, but, as the work progressed, so many different foods were shown to be the cause of a certain clinical disorder in some patient that it is now safe to say that there is probably no article of diet to which some one is not sensitive. One must remember, too, that not only foods, but anything such as drugs, vaccine, mineral waters, etc., taken by mouth may be the etiologic agent.

The study of patients where food sensitization is suspected may be divided into four steps:

1. History taking.

2. Examination (physical and laboratory).
3. Correlation and summation of information (diagnosis).
4. Treatment.

The history must be taken in great detail. If questions are properly directed the patient is often able to give definite clues that lead to the discovery of the causative agent. The food likes and dislikes must be considered. The complexity of the modern diet makes it necessary for the physician to have a wide knowledge of foodstuffs. The hereditary history may also be significant. The time used in taking a history is well spent and often a diagnosis may be made when this is completed.

Complete physical and laboratory examinations should be made. Coexistent pathology, although not directly related, may interfere with the progress of the patient unless it is corrected. In addition to the usual routine laboratory examinations skin tests should be made with all known food contacts. These skin tests should be made first by the scratch method and then, if indicated, by the intradermal method. The technic of making these skin tests is described in most textbooks on allergic diseases. The following precautions should be observed:

1. Always do the scratch test before attempting the intradermal test with any food.
2. Do not make too many tests by any method at one time. Some testing materials are much more toxic than others and some patients react violently to several allergens.
3. Do not make tests with most drugs by either scratch or intradermal methods.

The testing materials should be obtained from a reliable source and should be fresh enough to insure their potency. If clinical tests with suspected foods are to be done at all, they should be made cautiously as serious reactions may occur. Although some patients may be found sensitive to only one specific food most of them exhibit multiple sensitizations. Sensitization to additional foods occurs easily after the initial sensitization has developed. The size of the skin reaction does

not necessarily indicate the degree of sensitiveness. The correct interpretation of skin reactions can be made only by correlating them with the data obtained from the patient's history. This information, together with that obtained from the history and the laboratory and physical examinations, should enable one to make a tentative diagnosis. If the patient's progress is not entirely satisfactory, additional helpful information may be obtained by rechecking the history and skin tests. In some cases in which the skin testing has not given helpful information trial elimination diets may be used successfully. The following cases demonstrate different types of food allergy.

**Case I. Asthma.**—Male, age sixteen. Complaint when first seen at age eleven: perennial asthma for two years. Previous illnesses: chickenpox at five, whooping cough at seven, measles at ten. No eczema at any time. Tonsils and adenoids removed at six. First attack of asthma came on after exposure to road dust in summer. Subsequent attacks came on at frequent intervals, summer and winter, with and without exposure to dust. Certain foods had been suspected and taken out of the diet with only partial relief. The usual laboratory and physical examinations revealed no significant pathology. Skin tests, made by the scratch method, showed distinctly positive reactions to duck feathers, goose feathers, cat hair, and to the following foods; oat, rice, wheat, navy bean, string bean, lettuce, onion, pea, radish, spinach, banana, blackberry, cherry, lemon, plum, rhubarb, and black pepper. Following this examination feather pillows were discarded and all the foods that gave distinctly positive reactions were eliminated from the diet. Within a week all symptoms of asthma disappeared entirely. About six months later light attacks of asthma began to appear, although the outlined program had been followed faithfully. Skin tests were repeated. Several of the foods that had previously given large reactions now gave only questionable reactions, but three, celery, white potato, and peach, that had previously given no reactions gave distinctly positive reactions at this time. These three foods were eliminated

from the diet and all symptoms of asthma again disappeared. Six months later skin tests were made with all the foods that had given positive reactions at any time and of these only four, banana, peach, pea, and spinach, remained distinctly positive. These four were omitted from the diet and the remainder occasionally eaten in small amounts only. About one year later symptoms of asthma again appeared but disappeared when the stricter diet was followed for a short time. During the next three years all foods excepting banana, pea, and spinach were gradually added to the diet without causing any symptoms. Skin tests now show positive reactions for only these three and they are still strictly avoided.

This case record illustrates the following common characteristics seen in food allergy:

1. Multiple sensitizations.
2. Disappearance of symptoms following the elimination of the sensitizing foods.
3. Recurrence of symptoms when the diet is not strictly followed and when sensitization to new foods occurs.
4. The persistence of some sensitization for several years.
5. The gradual disappearance of sensitizations following strict adherence to dietary restrictions.

**Case II. Pollen Disease and Asthma.**—Female, age thirty-one. Complaint when first seen at age twenty-seven: autumnal pollen disease and asthma. When this patient was eighteen years of age she had her first symptoms of autumnal pollen disease and two years later had her first asthmatic attack in the last week of that pollen season. The hay fever and asthmatic symptoms gradually became more severe each succeeding year. Skin tests were made with all the pollens common to the Chicago territory. She gave large positive reactions to the pollens of the large ragweed, small ragweed, and burweed marsh-elder, and treatments by injection were started with an extract made from these pollens. As she gave such large local reactions with each injection we could increase the size of the subsequent dose very little and, as a result, her maximum dose

was only a fraction of that given to the average patient. The results from this treatment were not entirely satisfactory. The next season the treatments were started in April in an effort to increase the dose to a higher concentration of extract. Although a much higher dosage was reached this patient had much hay fever and asthma in September. The next spring skin tests were made with all common foods and other contacts. Corn, rye, banana, pineapple, asparagus, kidney bean, cabbage, and cottonseed gave distinctly positive reactions. Pollen extracts were again given as in the preceding year and in addition all the foods that gave positive reactions were eliminated from the diet three weeks before the onset of the pollen season in mid-August and this modified diet was continued until October 1st, the end of the pollen season. Although this patient remained in the same environment as in the previous years she had no clinical symptoms of hay fever or asthma. This was the first season of comfort since her symptoms started twelve years before. In this case the foods to which she was sensitive plus the inhaled pollen caused her to have symptoms in spite of adequate pollen therapy, and satisfactory clinical results from pollen therapy could not be obtained until the toxic foods were eliminated. During the past season the same program has been followed with completely satisfactory results.

This case record illustrates a very common complication of pollen disease (hay fever). In some cases the patients themselves have discovered that their symptoms from pollens are worse after eating some common food such as peaches or cantaloupe, but in most cases the relationship of foods to the symptoms has not been suspected. In some allergy clinics complete skin tests are routinely made in all cases of seasonal and perennial rhinitis. Complete skin tests should be made at least in all those patients who have not responded satisfactorily to adequate pollen therapy.

**Case III. Migraine and Pollen Disease.**—Female, age forty-two. Complaints when first seen at age thirty-six: mi-

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**Case III. Migraine and Pollen Disease.**—Female, age forty-two. Complaints when first seen at age thirty-six: mi-

graine since eighteenth year, grass pollen disease (rose fever) since eighteenth year. Attacks of migraine came at irregular intervals two or three times each month, summer and winter. Heredity: One half-uncle had hay fever and maternal grandfather had asthmatic bronchitis. Additional history not significant. Physical examination revealed no significant pathology. Skin tests made with all common foods, inhalants and other contacts gave positive reactions with all common grass pollens, and with one food, rye. The relationship of the ingestion of rye foods to the attacks of migraine had not been suspected as more or less rye bread was regularly used. However, this patient had observed that her attacks were always more severe while visiting a certain section of Canada and subsequent investigation showed that rye foods were extensively used there. Treatments were given with a grass pollen extract and all rye foods were eliminated from the diet. This patient has now been under treatment for six years and has had no symptoms of pollen disease and only an occasional attack of migraine when some rye food was knowingly or unknowingly eaten.

**Case IV. Urticaria and Asthma.**—Male, age fifty-seven. Complaint when first seen at age fifty-six: sudden severe attacks of abdominal pain, urticaria and asthma. For several years this patient has occasionally had severe abdominal pains which appear within one hour after eating and persist for one to two hours. Two or three of the more recent attacks have been accompanied by urticarial swelling of the face and trunk, nausea, vomiting, diarrhea and collapse. Except for these acute attacks this patient has been well. Skin tests made with all common foods, inhalants and other contacts gave typical positive reactions to sweetbreads, halibut, artichoke, paprika, and banana. The skin reaction to banana was very large and the patient admitted that he was fond of this food and frequently ate it liberally. Subsequently he exhibited a most severe attack after eating a portion of a banana. By eliminating all of these foods from the diet this patient was able to avoid the severe symptoms which frequently incapacitated him.

This case record illustrates some of the various symptoms which may follow the ingestion of some food to which one has become sensitized. In most cases of such sensitization the type of response is usually limited to one symptom, such as asthma, dermatitis, urticaria, migraine, etc., but in some cases two or more such symptoms appear in the same patient concurrently or alternately. In this case the sensitization to a food that had been eaten liberally since boyhood days did not occur until after middle life. Most sensitizations occur in the first decade of life.

**Case V. Asthma.**—Female, age thirty-eight. First seen at age thirty-seven with asthma. When this patient was thirty years of age she had her first attack of asthma following a severe chest cold. Following that attack she always had a few days of asthma with each fresh cold and after three or four years had frequent attacks in both winter and summer. She had learned from experience that she could precipitate a severe attack of asthma by taking acetosalicylic acid (aspirin) and would not use this drug knowingly. At the time of her admission skin tests made with all common foods, inhalants and other contacts gave reactions only to duck and goose feathers. Laboratory and physical examinations were made and no pathology was found except for evidences of infection in the sinuses and bronchi. Following the removal of feathers and the institution of conservative sinus treatments her symptoms became less troublesome but each fresh cold precipitated severe attacks of asthma. In the early stages of one of these colds she was advised by a friend to use one of the commonly advertised cold remedies. Within thirty minutes after taking the first dose she had such a severe attack of asthma that for hours her death seemed imminent. Investigation disclosed that the dose of cold remedy that she had taken contained about 2 grains of acetosalicylic acid. This case is cited to show that other things than foods taken by mouth may be the cause of asthmatic attacks. It is well to remember that several commonly used drugs may precipitate attacks of asthma or urti-

caria in those who are sensitized to them. The salicylates are the most common offenders and, as they are used in so many prescribed and proprietary medications, they should always be kept in mind when one is investigating an allergic patient. Quinine is probably the second worst offender.

**Case VI. Dermatitis.**—Male, age twenty-eight. When first seen at age twenty-six the complaint was dermatitis of the hands and face. This dermatitis first appeared when the patient was fifteen years of age and has been present more or less constantly since. He had worked at times in a bakery and thought that his lesions were more troublesome at such times, but they were present when he had no such exposure. Skin tests made with all common foods and other contacts gave distinctly positive reactions to corn, rye and wheat. These foods were eliminated from the diet and he avoided exposure by contact. The lesions gradually disappeared but would reappear if he ate cereal foods for two or three days in succession. For the past year he has been able to eat moderately of thoroughly toasted bread without causing any symptoms. In children and especially in infants cereal foods are more often found to be a cause of dermatitis than any other food. Citrus fruits are frequently the etiologic irritant in infantile dermatitis. Many bakers have dermatitis or asthma due to the ingestion, handling, or inhalation of cereal flours.

The most satisfactory method of desensitizing a patient to a food which has been shown to cause symptoms is the complete elimination of that food from the patient's diet. In some cases satisfactory desensitization may be accomplished in a few weeks while in others elimination of the food for years is necessary. Desensitization to eggs, for instance, usually requires a complete elimination of that food for years. In some cases of food allergy in children it may be necessary to eliminate the food from the home as traces of it may accidentally reach the patient. There are some who advocate desensitization in children by feeding small doses of a dilute solution of the food and increasing the strength gradually. This method has its limita-

tions and has not produced as satisfactory results as the complete elimination method.

Attempts have been made to desensitize by injecting an extract of the food subcutaneously but this method has not given satisfactory results. No attempts should ever be made to desensitize with drugs by the injection method.

In this discussion I have attempted to point out some of the salient features in the study of patients suspected of being allergic to foods. As has been stated the symptoms may be so varied and the causative agents so numerous that the relationship of the causative agent to the symptoms can be established only after a detailed study. The difficulties are greatest in those cases where multiple sensitizations are present or where there is an opportunity for exposure to unusual ingestants. In the daily life of the average inhabitant of a modern city there is a chance for exposure to about 150 different foodstuffs and in some cases the exposures are much above that number. In some special food mixtures there may be 10 or more individual foods. The discovery of the offending foods often enables the victim to change from a life of semi-invalidism to that of a comfortable self-supporting citizen. The time spent in solving problems of this sort pays comparable dividends.



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POLLINOSIS

**Historical.**—That hay fever is due to sensitization to pollens is not a new discovery. A very accurate description of the symptoms was written by Bostock in England in 1819. in an article entitled "A Case of Periodical Affection of the Eyes and Chest," published in the *Medico-Chirurgical Transactions of London*. John Elliotson, another Englishman, was probably the first to record pollen as the probable cause of hay fever in 1836. In 1873, Blackley undertook very accurate experiments to identify the grass pollens as a cause of hay fever. He undoubtedly was the first to make use of cutaneous reactions. Among the earlier students of this problem in the United States, mention should be made of Morrill Wyman, who in 1876 wrote a monograph on "Autumnal Catarrh" in which he accurately describes fall hay fever and ascribes its cause to the pollen of ragweed.

**Etiology.**—What is referred to in medical terminology today as seasonal pollinosis is known to the laity as "rose cold" or "rose fever," for the very obvious reason that the symptoms coincide with the blooming of the roses, or it may be referred to as "hay fever," if the symptoms happen to coincide with haying time.

The causative agent of all seasonal pollinosis is pollen, which is a light yellowish granular powder, the individual granules of which are microscopic in size, produced in the reproductive cycle of the causative plant whether it be a tree,

grass, or weed. It is rather obvious that this pollen must be light enough to be air borne in order that it may gain entrance through the respiratory tract.

**Quantity.**—The pollinating seasons of the various plants in this locality have been determined by field surveys and pollen counts. These pollinating seasons are given in the tables below. These tables are applicable to Chicago and its immediate environs. Similar surveys have been made for practically all areas in the United States and can be found in any standard text on allergic diseases.

### TREES

Common name.	Pollinating season.
(Major)	
1. Oak.....	May
2. Cottonwood.....	March to April
3. Ash.....	April to May
4. Maple.....	February to March
5. Elm.....	March
(Minor)	
1. Box elder.....	April
2. Walnut.....	May
3. Hickory.....	May
4. Sycamore.....	April to May
5. Tree of heaven.....	June

### GRASSES

Common name.	Pollinating season.
(Major)	
1. Bluegrass.....	May to June
2. Timothy.....	June to July
3. Orchard grass.....	May to June
4. Red top.....	June to July
5. Canada bluegrass.....	June to July
(Minor)	
1. Quack grass.....	June
2. Sweet vernal grass.....	May to June

### WEEDS

Common name.	Pollinating season.
(Major)	
1. Short ragweed .. . . .	August to September
2. Giant ragweed.....	August to September
3. Burweed marsh-elder.....	August to September



WEEDS (Continued)

Common name.	Pollinating season.
(Minor)	
1. Cocklebur.....	August to September
2. Lamb's quarters.....	July to September
3. Pigweed.....	July to September
4. Western water hemp.....	July to September
5. Russian thistle.....	July to September
6. English plantain.....	June to July
7. Tall wormwood.....	August to September

**Diagnosis.**—One of the most important steps in arriving at an accurate diagnosis of seasonal pollinosis is obviously an accurate history containing the date and place of the onset of the first symptoms. One should always inquire for dates and these may be most easily secured by asking the patient, "Did you have symptoms on Decoration Day or Fourth of July or Labor Day?" Or one may inquire where and when the patient was on his last summer vacation. Also, one should inquire as to the organs involved. Do the eyes itch, was there excessive lacrimation, was there itching of the nose, ears, or palate? How many handkerchiefs did you use? What was the character of the nasal secretion? Was it watery or mucoid, was it white or yellow? Do you suffer with tightness or wheezing in the chest? How many years did you have hay fever before asthma developed?

Now that we have established a definite season we must determine the causative factor or factors. This we do by testing with either dry pollens or extracts of the various trees, grasses and weeds which bloom during the period that the patient has symptoms.

**Methods of Testing.**—1. *Scratch or Cutaneous Method.*  
—To perform the cutaneous test for the sensitivity to pollen, small scratches are made, usually on the flexor surface of the forearm or on the back in the paravertebral region. These scratches do not have to be deep, but merely should break the continuity of the epithelium. When dry pollen is used, a drop of  $\frac{N}{100}$  sodium hydrate solution is placed on each scratch and then a small amount of dry pollen is added to each drop. These

tests can usually be read in from ten to fifteen minutes. A more convenient method for the scratch test is to apply drops of 1:50 pollen solution to these scratches. A positive reaction usually manifests itself by the formation of a wheal with a surrounding area of erythema.

While this method is a great aid in diagnosis of pollinosis in many patients, were we to depend upon it entirely, many diagnoses would be missed, as it is not an uncommon occurrence to find a patient who reacts not at all by the scratch technic but who still gives large reactions when tested by the intracutaneous method.

2. *Intracutaneous Method.*—With the intracutaneous method of testing we use a 1:1000 solution of the pollen and the test is performed with the aid of a tuberculin syringe and a 26-gauge short bevel needle. The site for the test which has been found most favorable is the extensor aspect of the upper arm. A very small amount of the test solution is injected intracutaneously and we do not attempt to measure this amount, but are guided by the small wheal which it raises and which is usually about 1 or 2 mm. in diameter. Occasionally a patient will not give positive reactions with a 1:1000 solution and we then test with a 1:500 solution, and if this proves negative we also test with 1:100.

3. *Conjunctival Test.*—If all these tests are negative and we still suspect pollen disease, we may perform the conjunctival test which consists of placing a small amount of dry pollen in the conjunctival sac and observing whether or not it produces a marked injection of both the palpebral and bulbar conjunctiva.

4. *Subcutaneous Injection Test.*—Another method of testing that has been used for patients refractory to cutaneous testing is the subcutaneous injection method where one injects a small amount of a more concentrated solution, 1:500 or 1:100, subcutaneously, and observes the patient for a systemic reaction manifesting itself either as hay fever, urticaria, or asthma, and also observing the site of the injection for a large local reaction.



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we deem it advisable completely to test all patients suffering with pollinosis. Only rarely does one find a patient sensitive to pollen only.

2. Inadequate treatment, that is, the patient reports too late for the dosage to be raised to an effective therapeutic level. or the treatment is stopped too soon.

3. The extracts used in the treatment may have lost their potency.

4. The treatment antigen may not contain the pollens to which the patient is sensitive.

**Symptomatic Treatment of Hay Fever.**—When the patient presents himself with symptoms of hay fever the following local measures in addition to the injections will give some additional relief. However, a word of warning regarding drugs in the allergic patient is not amiss. Before any drug is prescribed the patient should be questioned as to any known drug sensitivity. For the eye symptoms the following drops used in the eyes every two to three hours will allay the itching and relieve the inflammation.

R Epinephrine chloride 1:1000	.....	℥ x
Dilute acetic acid	.....	℥ iii
Resorcin	.....	gr. ii
Aqua dest ad	.....	℥ i

Many patients get adequate relief of their ophthalmic symptoms from the simple use of the eye cup with dilute boric acid solution or the solution of oxycyanide of mercury 1:5000.

For excessive nasal symptoms we use a 1 per cent aqueous solution of ephedrine hydrochloride as a spray every two to three hours. We have found that oily solutions are too irritating to the sensitive mucosa. For those patients who cannot tolerate ephedrine solution we use one of the ephedrine-like synthetic preparations. If the obstruction to nasal breathing is very marked, nasal packs with a good vasoconstrictor produce considerable relief. By mouth, ephedrine  $\frac{3}{8}$  grain combined with amytal sodium  $\frac{3}{4}$  grain or phenobarbital  $\frac{1}{4}$  grain, given in capsules every four hours, relieves the sneezing and nasal congestion.

The dosage is increased according to the following schedule which we have found most useful in that the volume of the individual doses is small. It must be realized that this schedule is very flexible and is modified for each patient.

DOSE SCHEDULE

Concentration 1 : 50,000	Concentration 1 : 5000	Concentration 1 : 500	Concentration 1 : 50
Dose No. 1—0.05 cc.	Dose No. 6—0.05 cc.	Dose No. 11—0.05 cc.	Dose No. 16—0.05 cc.
Dose No. 2—0.1 cc.	Dose No. 7—0.1 cc.	Dose No. 12—0.1 cc.	Dose No. 17—0.1 cc.
Dose No. 3—0.2 cc.	Dose No. 8—0.2 cc.	Dose No. 13—0.2 cc.	Dose No. 18—0.2 cc.
Dose No. 4—0.3 cc.	Dose No. 9—0.3 cc.	Dose No. 14—0.3 cc.	Dose No. 19—0.3 cc.
Dose No. 5—0.4 cc.	Dose No. 10—0.4 cc.	Dose No. 15—0.4 cc.	Dose No. 20—0.4 cc. etc.

The peak dosage in our clinic is the highest dose which the individual patient will tolerate. There is no fixed rule as to what this dose is and it is best determined by the physician who is treating the patient. However, we do not increase the dose beyond that which gives the patient the optimum of relief. This treatment just described is termed the preseasonal and coseasonal method because the patient begins his treatment twelve to fifteen weeks before the beginning of his particular pollen season. When a subpeak dose is administered at bi-weekly intervals throughout the year, and then gradually increased again preseasonally, it is termed the perennial form of treatment. The two-week interval is to be preferred because on this schedule constitutional reactions are less likely to occur. Constitutional reactions are controlled by the administration of epinephrine chloride in doses of from 0.5 to 1 cc., administered by hypodermic injection.

*Causes of Failure.*—The causes of failure in the treatment of seasonal pollinosis are:

1. Incomplete or inadequate testing, as the patient may be sensitive to foods or common inhalants such as orris root, feathers, cottonseed, insecticides, or animal emanations in addition to the pollen sensitivity. Therefore, to obviate this cause

we deem it advisable completely to test all patients suffering with pollinosis. Only rarely does one find a patient sensitive to pollen only.

2. Inadequate treatment, that is, the patient reports too late for the dosage to be raised to an effective therapeutic level. or the treatment is stopped too soon.

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Aqua dest ad	.....	℥ i

Many patients get adequate relief of their ophthalmic symptoms from the simple use of the eye cup with dilute boric acid solution or the solution of oxycyanide of mercury 1:5000.

For excessive nasal symptoms we use a 1 per cent aqueous solution of ephedrine hydrochloride as a spray every two to three hours. We have found that oily solutions are too irritating to the sensitive mucosa. For those patients who cannot tolerate ephedrine solution we use one of the ephedrine-like synthetic preparations. If the obstruction to nasal breathing is very marked, nasal packs with a good vasoconstrictor produce considerable relief. By mouth, ephedrine  $\frac{3}{8}$  grain combined with amytal sodium  $\frac{3}{4}$  grain or phenobarbital  $\frac{1}{4}$  grain, given in capsules every four hours, relieves the sneezing and nasal congestion.

For children from eight to twelve years of age the following prescription may be used:

Ephedrine HCl	...	gr. x
Elix. amytal	...	5 ss
Elix. lactopeptin	...	q.s. ad 5 iv

Sig.—1 teaspoonful every four hours.

Aspirin or combinations of aspirin with amidopyrine very often are helpful in allaying severe sneezing and nasal stoppage. If asthma complicates the hay fever symptoms, epinephrine chloride 1:1000 hypodermically in doses of 0.3 to 0.5 cc. repeated as necessary gives relief. Large doses of 1 cc. should not be used because of the toxic symptoms they produce such as tachycardia, pallor, fainting, vomiting and other symptoms of collapse.

Theophylline ethanol amine in capsules of 3 grains every three to four hours also has been found useful in asthma complicating hay fever.

Epinephrine 1:100 by inhalation has been disappointing in relieving asthma and we have discontinued its use.

The use of calcium, iodides, atropine and morphine for the relief of hay fever is mentioned only to condemn their use.

From the results we have seen, nasal ionization is apparently of no benefit in pollinosis. The same effect may be obtained with any escharotic such as 95 per cent phenol, strong silver nitrate, or the use of the actual cautery. Following ionization for pollinosis we have seen anosmia and neuritis of the nasal ganglion with severe pain following. We have also seen hyperesthesia of the sense of smell following its use. The use of nasal ionization should be discontinued in pollinosis. Pollinosis is a constitutional disease and should be treated as such. Any such severe local treatment to the sensitive nasal mucosa does more harm than good.

General measures such as avoidance of dust, swimming, exposure to the sun, heat and fatigue, golf and long automobile rides through the country should be followed. The diet should be carefully watched and all food allergens eliminated and the avoidance of all environmental factors such as orris root,



feathers, and other animal emanations should be carefully checked.

**Complications and Sequelae.**—The most common complication of hay fever which we see is pollen asthma. The usual history of this is that the patient has had pollen hay fever for several years and then suddenly developed pollen asthma. Usually the history is that two to three weeks after the onset of the hay fever in a certain year the asthma appeared. Occasionally we see the converse of this, in that the patient may have had pollen asthma for many years without ever having had any symptoms of hay fever. Obviously, the treatment of this pollen asthma is exactly that of pollen hay fever.

Another complication of pollen hay fever is pollen dermatitis. This may be either directly the result of sensitization to the pollen or it may be an old atopic dermatitis due originally to some other sensitivity but which has reappeared, apparently due to the pollen on either a specific or nonspecific basis.

Not uncommonly, there is a secondary infection superimposed on the pollen sensitivity resulting in a purulent sinusitis which may disappear at the end of the hay fever season or which may continue and become a most troublesome chronic affair. Commonly we see patients who at the beginning had only seasonal hay fever but who gradually developed what we call perennial allergic rhinitis. Similarly, we find cases of perennial asthma which started out as purely seasonal affairs but with each succeeding year the symptoms of the asthma persisted longer, until finally it was a perennial type of asthma.

The other sequelae of untreated asthma are too well known to receive any special comment other than the mention that these are emphysema, chronic bronchitis, deformity of the chest, and at times even bronchiectasis.



## CLINIC OF DR. FRANCIS L. FORAN

### ALLERGY CLINIC OF RUSH MEDICAL COLLEGE OF THE UNIVERSITY OF CHICAGO

#### THE ALLERGIC FACTOR IN MIGRAINE

It is not within the scope of this clinic to attempt even the most general discussion of the ancient riddle of migraine or of the modern riddle of allergy. But for the sake of clarity a brief definition of terms is desirable.

Migraine is a syndrome of severe headache, paroxysmal and recurrent, commonly unilateral, occurring usually in association with cortical symptoms (sensory, motor, or mental) and nausea or emesis. An enormous literature has produced a multitude of hypotheses. Outstanding is the striking influence of heredity. This fact together with the frequent occurrence of frank allergies in the individual or his family led Vaughan and numerous other authors, mostly in the past decade, to elicit evidence of allergy as a factor in migraine.

Allergy commonly connotes a demonstrable hypersensitiveness with an immunologic mechanism. However in its original coinage and wider sense the term simply implies an altered reactivity, an exceptional and inimical response of the organism to contact with substances in themselves usually innocuous or salubrious. In this extension the concept has the virtue of taking cognizance of certain striking clinical sequences, presumably of cause and effect and not otherwise classified, but the defect of supplying no *modus operandi* for their occurrence. There is impressive evidence that in this wider sense at least many cases of migraine are definitely allergic, with the reservation, however, that allergy is not usually the sole factor in their genesis.

**Case I.**—Migraine in a patient without other major allergy.

A. B., female, age twenty-six, single, clerk in a social service organization.

*Family History.*—There is no known case of epilepsy or insanity in any branch of relationship. The paternal grandmother died of "asthma." The father, deceased, was said to have had frequent headaches. The mother, still living, after her menopause developed periodic headaches which usually appear on awakening and are relieved by vomiting.

One brother had infantile eczema but no headache. Two sisters have neither headache nor allergy of any type. One cousin has eczema but no headache.

*Duration and Course.*—As a child the patient recalls widely separated attacks of sudden intense headaches with vomiting and visual disturbances.

Five years ago, at the age of twenty-one, the patient had a severe obscure illness ultimately diagnosed as tuberculous peritonitis. During convalescence the headaches became of frequent occurrence averaging once to several times a week.

*Character of Attack.*—The pain is located most intensely in the right occiput radiating thence over the entire head. It begins as a throbbing, developing into a heavy pressure or sense of expansion. The attack lasts usually a day but not infrequently continues for several days, the longest having been nine days in duration.

Nausea and emesis are not invariable accompaniments, but violent and persistent vomiting frequently occurs. The vomiting aggravates rather than relieves the headache. Hunger and abnormal appetite are often present during the attack. Violent sneezing, sometimes to the point of epistaxis, occasionally attends the headache. At other times the patient has morning sneezing without associated headache. This latter is the only symptom suggestive of other allergy in the patient.

*Aura and Cortical Symptoms.*—Usually before the pain begins the patient notices a blurring of vision and a sense of mental "heaviness" which seriously impairs her power of attention. These symptoms become very severe during the painful phase and continue on the day following.

*Precipitants of Attack.*—The menstrual period bears no constant relation to the headache. Neither mental nor physical fatigue seems to cause an attack. Prolonged use of her eyes does not occasion a headache despite the visual obscuration which attends the attack. Movement aggravates the headache once it has begun and a long ride on street cars seems to start a minor attack.

*Food Precipitants.*—The patient's own observation has established the striking relationship to specific food ingestion. Asparagus has repeatedly precipitated attacks. Chocolate, peanut, and tomato are also certain excitants. Two instances of her food sensitiveness were recently noted. On the occasion of testing the patient's leukopenic index to the ingestion of chocolate a large piece of chocolate was eaten at 9.15 A. M. At noon the patient felt "light-headed"; at 2.00 P. M. occipital headache had begun and at 3.00 P. M. she could not see clearly. At 3.00 A. M. the following morning she vomited without relief. The headache slowly abated the following day. Recently, while at a picnic, the patient had an attack which she attributed to the ride on a street car. On cross-examination, however, it developed that the patient had eaten a peanut butter and jelly sandwich. Despite her own observation on the rôle of peanuts in her migraine, she had overlooked the possible importance of the peanut butter.

*Skin Tests.*—Scratch tests with about 80 proteins including the implicated foods were entirely negative. Intradermal tests gave an indecisive borderline reaction to chocolate.

*Leukopenic Index.*—This was carried out with milk and chocolate taken on a fasting stomach as follows. White counts were made by the same technician using the same pipet, just before feeding the patient the tested food and at twenty-minute intervals thereafter. The results are shown in the tabulation.

*Comment on Case I.*—We have here a typical migraine of which the only known etiologic factor appears to be the ingestion of specific foods.

The skin testing was of little assistance in furnishing either new or confirmatory evidence. The leukopenic index gave a

## TABULATION

Time.	Leukocytes.	Polymorpho- nuclears.	Lympho- cytes.	Monocytes.	Eosino- philes.
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Milk tested: 6/17/36. Nonallergic response.

9.15 A. M.	7250	53	39	3	5
9.20 A. M.	Milk—8 ounces ingested				
9.40 A. M.	6450	55	35	6	4
10.00 A. M.	7950	61	34	4	1
10.20 A. M.	6950	54	38	0	7

Chocolate tested: 6/20/36. Allergic response.

9.15 A. M.	7000	48	44	4	3
9.20 A. M.	Chocolate ingested.				
9.40 A. M.	6750	37	52	5	6
10.00 A. M.	6450	59	31	5	5
10.20 A. M.	5150	61	29	6	4

The leukopenic index was developed by Warren T. Vaughan after observation of the leukocytic response to the ingestion of food by allergic subjects. A non-allergenic food usually causes a postprandial leukocytosis; an allergenic food, a leukopenia. A variation of less than 1000 cells above or below the fasting level is regarded as an indeterminate finding.

fairly typical curve indicative of allergy to chocolate. Differential counts were added for their general interest. There have been some observations on eosinophilic variations but thus far the emphasis has been placed on the total leukocyte counts. A more extended use of the leukopenic index, especially in the skin-negative cases, promises improved results. Nevertheless the weight of the inquiry is borne mainly by the anamnesis and clinical trial.

Our service to the patient consists in putting proper emphasis on the food factor. Further supervision may elicit more information. Foods biologically related<sup>1</sup> to those known to be implicated will be held under suspicion. Thus susceptibility to peanuts will suggest the alternate trial and elimination of other legumes, such as peas, lentils, and beans; to asparagus, of the

<sup>1</sup>Ellis, Ralph V.: A Rational Grouping of Food Allergens. J. Allergy. 2: 246, 1931.

liliaceous vegetables, onion and garlic; to tomato, of the solanaceous vegetables, potato and peppers.

At present while the attacks have been reduced in frequency, many occur without a recognized occasion of food ingestion or indeed of any cause.

**Case II.**—Migraine in association with hay fever, pollen asthma, urticaria, and an anginoid syndrome to drug ingestion.

R. B., male, age thirty-two, single, an unemployed machinist's helper.

*Family History.*—The father and paternal grandmother had asthma. Both the father and mother had "sick headaches" with vomiting. Two sisters have attacks similar to his own and one has asthma also.

*Duration and Course.*—In childhood the patient had a few attacks a year and at the age of eighteen the frequency increased to about twice monthly.

*Other Allergies in the Patient.*—About ten years ago the patient developed a ragweed seasonal hay fever with severe asthma. These symptoms have been much curtailed by hypsensitization treatment in the past four years. Sharp skin reactions to pollen have been repeatedly obtained. It is deserving of particular comment that the headaches are not aggravated in the pollination season.

An attack of giant hives and severe asthma followed the ingestion of brazil nuts about six months ago. Again it is to be noted, that only a slight headache attended this attack.

The ingestion of aspirin, formerly taken for the headache, uniformly was the occasion for a precordial pain radiating down the left arm to the wrist. Ephedrine, used recently, not only moderates the headaches but, by the patient's volunteered statement, "has a quieting effect on the heart."

*Character of the Migraine.*—A recent typical attack was described thus: about four hours after eating some sausage meats, he had "gas" and "felt nervous." Shortly after headache began over the right eye gradually spreading down to the right ear. In a few hours vomiting of fluid material with no

food residue and without relief of the headache occurred. After about six hours the attack abated.

*Food Precipitants.*—All meats of the ungulate order but especially pork occasion headache. Chicken also to a somewhat less degree. Cured meats are tolerated better than fresh, and ham is sometimes eaten without sequel. Chocolate and beans are other known offenders.

*Other Precipitants.*—The patient has attacks very definitely occasioned by causes other than foods. Any nervous excitement, even such as a prolonged conversation, is likely to be followed by headache. Exposure to heat, sun or bright light are other occasions.

*Skin Tests.*—Scratch tests were entirely negative to all foods. Intradermal tests gave borderline positive reactions to chocolate and pork.

*Comment on Case II.*—Noteworthy in this case are the diverse manifestations of hypersensitiveness and the diverse nature of their occasions. The substances causing headaches do not cause asthma or urticaria and the reverse statements also hold. A pollen inhalant causes asthma and hay fever; a drug ingestant, angina; a food ingestant, urticaria and asthma; and still different food ingestants, migraine.

A diversity of mechanisms is also presumptive. Despite the evidence of the patient's atopic reactivity as seen in the positive skin tests to pollen, the foods definitely causative of the migraine give negative or indeterminate tests.

The therapeutic response to ephedrine is of interest. Despite the known sympatheticomimetic action of the drug, it has apparently a sedative effect on the "nervousness" incident to this migraine.

The case furnishes a good instance of group sensitization, in that the meats of the ungulates, beef, lamb and pork, all cause headache. A relative tolerance to the implicated meats after they have been cured is of practical significance. Food processing in either commercial or domestic preparation may be of advantage in the therapeutic management of allergies. The "hypo-allergic" milk of commerce makes use of this fact



and condensed, powdered, or malted milk may serve the same purpose. Heat by boiling, cooking, baking, or toasting in the home may modify the specific reactivity of a food protein.

It should again be noted that the food idiosyncrasy is simply one of several known excitants of the migrainous attack.

**Case III.**—Migraine in association with gastro-intestinal allergy.

A. J., male, age twenty-six, married, a medical student.

*Family History.*—His father and mother have no evidences of allergy. One brother who has urticaria, a chronic sinusitis and frontal headaches, gives positive skin tests to banana and tomato. One sister is very sensitive to strawberries and house dust, has dermatographia and urticaria but no headache. A second and third sister have migrainous headaches from milk, fish, and meat and are said to have given positive skin tests to these substances.

*Patient's Allergy.*—Several hours after the ingestion of milk the patient develops a unilateral headache. Some hours later a severe diarrhea follows.

A quantitative factor is present. A single glass of milk may be taken usually without symptoms. In this case, however, condensed or boiled milk will produce the same effect as the raw milk.

*Skin Tests.*—The scratch tests were entirely negative. Milk gave a negative intradermal test also.

*Comment on Case III.*—The negative skin tests in this patient are in contrast to the reported positive reactions of his brother and sisters. Whether this apparent variation is due to differences in technic, interpretation, or basic mechanism cannot now be said.

The quantitative factor may often be of importance in balancing a dietary with essential food elements. By not exceeding the level of tolerance, complete elimination may be avoided. The relation of quantity to the periodicity of symptoms was brought to attention in another instance. A school principal had been having migraine recurrently on Sunday

morning, which paradoxically he related to his week-end relaxation. After elimination diets had established wheat as a causative factor the periodicity was explained. The patient was in the habit of having a midnight supper largely of sandwiches on Saturday night; during the week, however, he ate very sparingly of bread and other flour products.

**Discussion.**—These cases are illustrative of the striking association of allergy and migraine in the individual or his heredity or both. The familial incidence has been estimated at 51 per cent (DeGowin), and where migraine is counted as an allergic characteristic, the family history shows upward of 80 per cent allergy (Sheldon and Randolph). The incidence of collateral allergy in the migrainous individual has been estimated at from 45 per cent (Westcott) to 80 or 90 per cent (Vaughan).

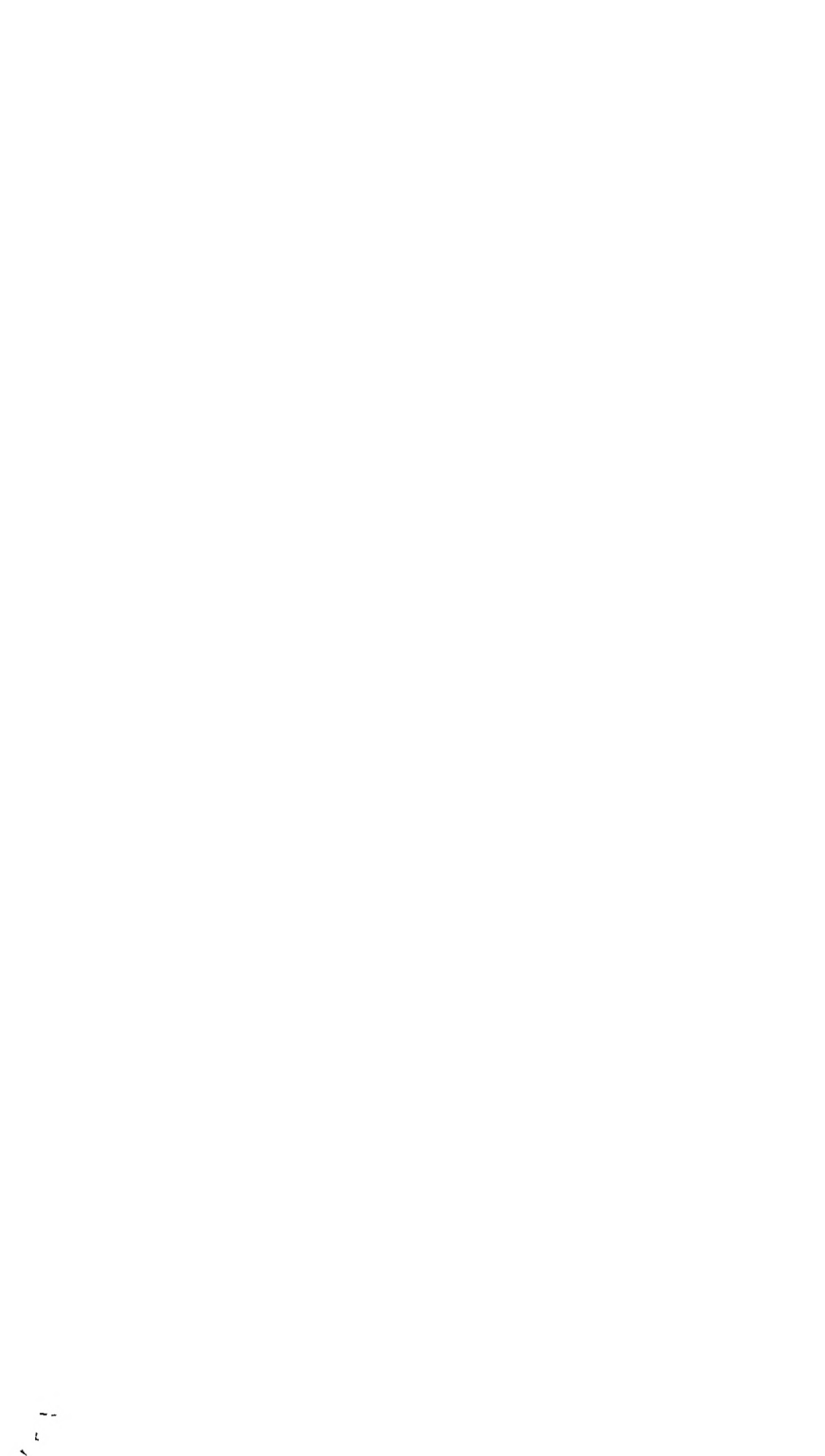
The repeated demonstrations from many sources of the sequential relationship of migraine to specific food ingestion would seem too definite to be mere coincidence. The presence of such an allergic factor in migraine has been set at from 35 per cent (Westcott) to 70 per cent (Vaughan). We have been impressed in this clinic, however, that, even in the presence of definite food specificity, there are usually other exciting factors of the migraine syndrome.

Skin testing has not been a productive procedure in our hands; in contrast to its great diagnostic value in asthma, hay fever, and eczema, it has given meager information in migraine, comparable to its very limited value in urticaria. This is in accord with the experience of Rowe but many careful allergists of wide experience report otherwise. Vaughan found skin tests a reliable lead in 50 per cent of his cases. It may well be that migraine is caused in some instances by an atopic and in others by a nonatopic mechanism. On the basis, therefore, of general experience thorough skin testing should be routine.

The leukopenic index has much promise as a diagnostic aid. Careful history taking, the use of the food diary and trial diets are of prime importance in diagnosis and confirmation of food sensitiveness.

The preponderance of certain foods as migraine excitants is of interest. A compilation was made of the first dozen foods in the order of their importance reported by six different authors (Vaughan, Alvarez and Henshaw, Sheldon and Randolph, Westcott, DeGowin, and Eyerman). An analysis shows that onion appears in 5 lists; cabbage, chocolate and pea, in 4 lists; coffee, egg, milk and wheat, in 3 lists; apple, beef, cantaloupe, celery, cucumber, orange, peanut, potato and tomato, in 2 lists. The following foods appear only once: banana, beans, carrot, chicken, lettuce, nuts, oat, peach, pork, radish, sweet potato, tea, veal, watermelon.

**Conclusion.**—An impressive mass of clinical data supports the contention that migraine is often occasioned by specific food ingestion. In this sense at least an allergic factor is demonstrated. The mechanism of its action and the extent of its significance in the total problem of migraine are still matters of dispute. But the statement is conservatively warranted that allergy has brought to the solution of this neurological enigma a contribution of real value.



## CLINIC OF DR. JOSEPH BRENNEMANN

### THE CHILDREN'S MEMORIAL HOSPITAL

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#### CELIAC DISEASE

It may seem a bit startling to find a young lady of eighteen in a pediatric clinic. There are, however, certain diseases in which a presentation of the end-result and all that has led up to it is as instructive as the demonstration of a like case would be in the earlier, active stage. This is perhaps especially true in that of the young lady before us whose history is an epitome of a disease that is rare; that was once, I think, more frequent: that presents during the active period a striking, easily recognizable, clinical picture concerning the actual etiology and pathogenesis of which we are still quite in the dark; that formerly had a high mortality and, at best, led to years of profound nutritional and emotional disturbances; that in spite of our lack of knowledge as to the underlying cause and nature of the disease can now be cured within a reasonable time with a fairly full assurance of success. This is all the more interesting because the treatment is wholly dietetic. To one familiar with the disease it is probably evident from what has been said that we are dealing with celiac disease. You will come across it in the literature under a variety of names, of which only Herter's infantilism, and the German, *die Coeliakie* and *Chronische Ehrnährungs-störung jenseits des Säuglings Alters* need here be added to the English "celiac disease," introduced by Gee who first described the disease in 1888. It is essentially a pediatric disease, always beginning in late infancy or earliest childhood and rarely extending in an active form to adolescence.

As I have implied, this girl, in her own case, unfolds practically the whole story of celiac disease, individually and his-

torically, from the time when we stood almost helpless before a case and dreaded to see one up to the present time when the outlook is favorable enough for us to welcome each new one.

Before entering upon that story let us briefly see the end-result—itself interesting because still somewhat in dispute. It is evident from “Herter’s infantilism” that retarded growth was considered a part of the picture. A marked retardation of growth is always evident during the active stage and when this is prolonged the stature remains permanently below normal. It remains to be seen what the result will be in those patients in whom convalescence can now be reached so much more quickly than in former times. This girl presented an extreme picture of the disease. The active period lasted from the second to the sixth or seventh year, and, because of home conditions, progress was variable for some years longer. One has the impression that she is still undersized and yet, as you see, she is nearly as tall as her mother. (Another patient whom I have been able to follow to adolescence under more favorable surroundings is practically of normal height.) She is fairly well proportioned with a distinct tendency to obesity, a frequent end-result, and has a rather prominent abdomen that is a remnant of a condition that is one of the most striking and characteristic features of the earlier active stage of the disease. Her mentality is apparently somewhat below normal. During the early part of her disease this was a marked feature, her psychic response varying directly and proportionally with her physical state. In general children with celiac disease are normal mentally. Some have even thought them to be above average in that respect. The only other evident result in this instance is extreme dental caries that involves practically all of her teeth, most of them decayed flush with the gums.

Our patient was born March 16, 1918, and entered the Children’s Memorial Hospital for the first time December 18, 1920, at the age of two years and nine months. Because of language difficulties and ignorance on the part of the parents her early history was only vaguely obtainable. As nearly as could be ascertained she had had a diarrhea with some vomiting

for a period of six months or more. The stools were loose and pale, from 2 to 5 or 6 a day. The food was said to "pass through undigested." During this time there was a steady and very great loss in weight, the child slept poorly and could no longer walk or even stand alone. Her weight on admission was 15 pounds, about what we would expect a normal five months' old baby to weigh.

The general appearance was that characteristic of an advanced stage of the disease. There was extreme emaciation on the one hand and an enormously widely distended abdomen on the other. The child was pale and apathetic, except over the abdomen the skin was loose and unfilled because of the flabby and atrophied musculature and, even more, because of the almost complete absence of subcutaneous fat. The emaciation was especially marked in the extremities and in the gluteal region. The wasting of the buttocks has been given diagnostic significance by Miller as the "gluteal sign." It is only natural, however, that with a generalized loss of fat its absence should be most noticeable where it is normally most in evidence. The face often remains fairly filled out in contrast to the rest of the body, but in this child it was involved to a like degree. The skin hung in folds and the eyes appeared unduly large. There was no normal play of expression. She was wistful, pathetic, not happy rather than acutely unhappy, with no evidence of pain except when disturbed. The latter was probably due to latent scurvy, or possibly neuritis, which may accompany the disease in varying degree for obvious reasons. An evident tetany, a frequent accompaniment, doubtless played a part. The extremities were flexed at the elbows and knees and there was marked carpopedal spasm of both hands and feet. The Chvostek facial sign of tetany was present.

The teeth showed widespread caries. The hemoglobin was reported as 75 per cent; the red blood cells as 4,000,000; the white blood cells as 10,200. The temperature was subnormal.

The abdominal distention was perhaps the most arresting feature of the whole picture. The abdomen seemed out of all proportion to the rest of the body, not especially tense, not

tender, but extending in all directions as if pushing other structures out of the way. In spite of the thin wall there was no evidence of an intestinal pattern—hence no increased peristalsis. The distention was evidently due to hypotonicity of the intestinal and abdominal walls and the presence of an abnormal amount of gas in the intestinal tract, both a cause and an effect. It was natural that the intern should record his impression that the child had a tuberculous peritonitis, a mistake that is probably made at some time in nearly every case. Tuberculin and Wassermann tests were negative.

The diagnosis of celiac disease ultimately rests on the nature of the stool, the color, odor, consistency and volume of which are pathognomonic in the proper clinical setting. The stool is always grayish-white in color and has usually a degree of foulness rarely attained by any other. Its advent is evident in the room and nurses are loathe to save the stools even in a closed container. They may be hard and formed and reduced to 1 or 2 a day during periods of more favorable progress; or frequent, soft and mushy during periods of exacerbation that are so prone to occur, often inexplicably. They rarely exceed 4 or 5 a day. They have a greasy appearance at all times, notably so when loose. They then resemble oatmeal porridge as long ago pointed out by Gee whose classical description has left little to be added. More striking than anything else is the amount of stool passed in the twenty-four hours. This often exceeded more than a pound a day in our patient. Freise and Jahr reported eight to ten times as much stool in 2 children with celiac disease as in two normal controls on the same intake of food. All of these characteristics are evidently due to non-absorption of fat.

During the first seven months in the hospital the condition remained practically unchanged. All sorts of things were tried, both empirical and seemingly rational in our then current state of knowledge, without tangible progress. Finally, each new resident took a fling at it in the light of what he had been taught in school or in some other medical center. Characteristically, things got alternately better and worse. Tetany



was present at times and again absent. The disposition varied with the nature and frequency of the stools, a pretty accurate barometer of progress. Her weight varied from 15 to 16 pounds and when it once got up to 17 pounds and her stools were formed and reduced to 1 a day, she was allowed to go home.

Five weeks later (8/24/21) she was readmitted. During the stay at home there had occurred one of those catastrophic losses in weight and general well-being that are so frequent in these patients following errors in diet, often enough without evident reason. She had lost 4 pounds and now weighed 13 pounds, pretty nearly an all time low for a child of three and one-half years.

In June, 1921, Dr. John Howland delivered his presidential address before the American Pediatric Society on the subject of Prolonged Intolerance to Carbohydrates. Unfortunately, but characteristic of the man, this paper was allowed to remain buried in the Transactions of that Society from which it has only been exhumed from time to time by those especially interested in the literature of celiac disease. Contrary to the prevailing view that celiac disease was due to an inability to digest and utilize fat, Howland pointed out, based on a study of more than 30 cases, that the essential trouble was a chronic intolerance for carbohydrates. As a natural corollary he advocated a dietetic régime of 3 stages, each varying in length according to the severity of the disease and the reaction of the child:

1. "Protein milk alone until the stools are firm, the distention very slight, the gas not in excess and the appetite good."
2. Protein milk with the addition of "curd, scraped beef, certain forms of cheese, egg white and eventually the whole of egg" and "some orange or tomato juice."
3. The cautious addition of vegetables well puréed, first the 5 and then the 10 per cent types, followed as tolerated, finally, by bread, cereals and potato.

Profoundly impressed by this paper we put our patient on a high protein daily diet of a quart of protein milk, scraped beef, eggs (soon discontinued), diaprotein muffins and small amounts of vegetables, fruit and bread. It will be noted that,

through a misinterpretation, this diet did not conform to the fundamental ideas advanced by Howland in that a small amount of vegetables, fruit and bread were permitted. Too, we erroneously thought that our patient was old enough not to require a rigid adherence to so limited a diet. She was kept on this diet with occasional variations for about a year. In the first month she was greatly improved and gained  $4\frac{3}{4}$  pounds, up to  $17\frac{3}{4}$  pounds. The next month she lost  $2\frac{1}{2}$  pounds. Her weight fluctuated widely for the rest of the year. Toward the end of the year she was put on a general diet, advocated at the time by certain German clinicians. The stools rapidly became loose and more frequent, there was a sharp drop in weight and at the end of that period she weighed only 16 pounds at four years and seven months of age.

She was now put on a rigid high protein diet—or, I would prefer to say, *on a minimal carbohydrate diet*. This consisted of protein milk (with occasional change to buttermilk), scraped beef, diaprotein muffins, gelatin and cottage cheese, of each as much as she cared to eat. The clinical note soon reported: "She relishes this diet and the stools begin to improve." Her disposition changed; she became happy, and talked and played with other children. On this rigid diet for seven months her stools remained at 1 or 2 a day, were formed but still large and rather offensive, and her monthly gains in weight were 2, 2, 2, 2, 2, 2, and 3 pounds. In seven months she had nearly doubled her weight, going from 16 to 31 pounds.

One cereal a day was now added to her diet. There was a prompt return of loose, more frequent, greasy stools and a drop, or rather a downward push, of 2 pounds in weight which she only regained after another two months. Progress notes at this time reported her to be: "rather pale, not so active, losing weight; stools much softer and of lighter color. Patient has been acting drowsy, toxic. Chvostek sign positive." On returning to the previous rigid diet plus 3 bananas daily, she gained rapidly as shown by monthly gains of 3, 2 and 1 pounds. In spite of the serious setback she had gained 19 pounds during the year, going up from 16 to 35 pounds. Two years later she

was discharged at the age of seven years, eight months, weighing 48 pounds. Her last record, four years later, showed her weight to be 63½ pounds and her height five feet, one inch. She was then eleven and one-half years old. During the latter part of her stay in the hospital she was gradually switched to a general diet which was continued at home. Only minor upsets occurred during this time. Her condition since that time has been much as you see it now.

What do we know about the nature of this strange disease? Necropsies have thrown practically no light on the subject. Some of the reports have been wholly negative, others contradictory, and one rather gets the impression that such findings as atrophy of certain viscera, of the intestinal mucosa, etc., are an effect, not a cause. From the gross appearance of the stools and from microscopic and chemical analyses it was evident that these were largely made up of fat derivatives. It was natural to assume that we were dealing with a chronic fat intolerance. It was natural, again, to assume that there was basically a pancreatic deficiency. This seemed improbable, however, inasmuch as the disease was always preceded by a normal condition and, under favorable conditions, a full normal state recurred. It was even more negatived by the fact that while in a pancreatic deficiency the fat is not split, it is in celiac disease. In the latter neutral fats, fatty acids and soaps are all found in such amounts that they determine both the characteristic consistency and the abnormal volume of the stools. So great is this volume that it has even been held that there was an endogenous transfer of fat from the body into the intestinal canal, but this lacks support. Whatever the pathogenesis of the disease may be, the fact stands out that the fat is not absorbed normally. Why, no one knows.

Attempts have been made to solve the problem by a study of the intestinal bacterial flora, notably by Herter who published his results under the title of Intestinal Infantilism in 1909. Based on the fact that he found a predominantly gram-positive flora made up of *Bacillus bifidus*, *Bacillus infantilis* and gram-positive cocci which normally characterize the intes-

tinal flora of the breast-fed infant stool, he postulated the persistence of this condition into the artificially fed period as the cause of celiac disease. This view no longer has any adherents. The endocrines, the sympathetic nervous systems, an abnormal constitution, a neuropathic state, dysentery, acholia and avitaminosis, have naturally all been drawn into the picture as interesting but futile speculations.

The observations of Howland, that led to the view that there was essentially a chronic carbohydrate intolerance, have appealed to me as basic and my own experience and a perusal of the literature has not changed that view except in minor respects. I have not adhered to a graduated 3 phase diet but have put even infants (the disease rarely begins before the second or third year) on as nearly a carbohydrate-free diet as can feasibly be devised and can only say that for the first time in my experience this furnishes a régime that has uniformly led, sometimes to wavering, but always to satisfactory results and to a fairly early cure. That fresh whole milk is not tolerated has long been known. That the fat is not the basic noxious agent would seem evidenced by the fact that protein milk is well tolerated in spite of the fact that it has a fat content comparable to that of whole milk. That there is no danger of carbohydrate starvation on a high protein diet was emphasized by Howland in that an adequate amount of carbohydrate is derived from the protein. Evidence has been presented by Nelson that dextrose is tolerated in large amounts, in direct opposition to a statement by Howland that it is not. I have had no experience on which to base an opinion but am inclined to accept Nelson's conclusions. There is practically no dissent from the view that starch is the one dangerous food element and that starchy foods must only be introduced after convalescence has long been established and even then with great caution.

My own procedure in recent years has been as follows: As the liquid food I give protein milk as much as the child will take at the usual intervals. Buttermilk may be given equally well for a time. No carbohydrate is added; if sweetening is

needed a grain of saccharine is added to a quart of either food. Slightly broiled scraped beef is offered three or four times a day at the usual feeding times. To this are added, *ad lib.*, cottage cheese, gelatin, egg white and muffins made of diaprotein or other low-carbohydrate flours, 2 or 3 ounces of orange juice and a teaspoonful of cod liver oil, or an equivalent amount of viosterol or percomorph oil. If tolerated 1 to 3, or more, bananas are added. These must be fully ripe, mealy, with black or black-dotted rinds. There is usually an almost immediate improvement in the nature of the stools, the gain in weight and the child's disposition. After a variable time, usually a matter of months, puréed vegetables and fruits are added with due caution. Still later toast, and lastly starchy foods such as cereals, usher in a general diet, including boiled, or evaporated milk. Vigilance must still be maintained. The general dietetic dictum, "advance slowly, retreat precipitously," is nowhere more applicable than here. Drugs play no part, except the occasional indication for iron. Transfusions may help, but are rarely necessary. Ultraviolet rays are valuable if cod liver oil is refused, or not well tolerated.

Other methods of treatment have been advocated. Haas has especially popularized the use of bananas as a sort of basic diet and has given as many as 16 a day to a child. Bananas are undoubtedly well tolerated in many, probably most, cases and are therefore a valuable addition. This has been confirmed from many sources. Celiac disease is, however, a very notional disease, has possibly not a unitarian etiology, and the banana is not a specific. As in the use of all other foods caution must be observed and theory and authority may have to give way to experience in the individual instance.

Celiac disease is a rare disease and I have had no occasion to try out the more rigid fruit and vegetable cure of Franconi. This consists in giving first the juices of oranges, lemons, berries, grapes, etc.; later, bananas, scraped apple, pears, etc.; and still later, puréed vegetables, all in gradually increasing amounts. Cane sugar and starchy foods are considered harmful even in small amounts. Good results are reported on this régime.

Many Continental observers have advocated a liberal general diet, with few interdictions. I rather think these views hark back to a time when we knew less than we do now about the treatment of celiac disease and were satisfied with less assured results.

As a curiosity, it would seem to me, may be mentioned finally the *Übungs Diät* (exercise, or stimulation, diet) of Schick and Wagner. This consists in giving just the articles of diet that are not, or poorly, tolerated with the idea of stepping up the tolerance by exercise, or stimulation, of the digestive glands involved. A reported mortality of 40 per cent in 5 cases hardly furnishes an incentive to try this unique procedure!

In the treatment of diseases that are rare and, in the past, have been discouraging—not to say baffling—we are prone to follow a course that we have found leads to results. For that reason I still use a high protein diet, or rather a low carbohydrate diet—or still more specifically, as a desideratum, a starch-free diet.

## CLINIC OF DR. FRED M. DRENNAN

### MERCY HOSPITAL

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#### AMEBIC DYSENTERY

I AM going to start this clinic with a brief history of the case being demonstrated as it is fairly typical.

A young man, twenty-eight years old, came to my office a few months ago complaining of diarrhea. His work has been that of a salesman in the southern part of the United States. While in North Carolina, six months previously, he had been "upset by food" taken and had a severe though short duration diarrhea with abdominal cramps, tenderness, nausea and vomiting, mucus but no blood seen in the bowel movements. He did not know about temperature but felt he probably had no fever. He felt weak and "played out" but went on about his work and in a few days was seemingly all right. Following this, he had recurring short duration diarrheal attacks becoming more frequent, so that during the two months before examination he had continual loose movements, three to six daily, watery in consistency, with associated rumbling and gurgling, cramp-like pain at times severe during defecation, marked generalized abdominal tenderness, mucus and blood in the bowel movements. There was only a slight loss in weight, though he felt tired and worn out. He complained of nausea and lack of appetite, but had no vomiting after the first attack.

At our examination the blood pressure was 114/86, temperature 98° F. Urine was negative as to albumin, sugar and casts. Hemoglobin was 80 per cent. Ewald meal showed free acid 45, total 81; benzidine test for blood negative. Bowel movements were mushy to watery, and on examination showed benzidine ++++. Physical examination was essentially

negative except for a markedly spastic, ropelike, and tender colon. Rectal examination caused no particular pain, and no masses were felt. A second stool examination showed mucus and blood; on warming specimen for microscopical examination amebic organisms were demonstrated.

A clinic on "amebic dysentery" is always an interesting subject for the teacher because it must deal with a condition concerning which medical investigation has had a great deal of uncertainty. In this clinic I am going to mention only things that seem at the present time to be fairly stable.

By the term "amebic dysentery" we mean a disease caused specifically by the *Endamoeba histolytica*, the lesions originating and being chiefly in the large intestine though liver complications are present; clinically characterized by diarrhea with blood, pus and mucus in the bowel movements. There is a tendency for the symptoms to be intermittent which perhaps increases the difficulty in diagnosis, the locating of carriers, and the development of complications. Many cases are seriously disabling if allowed to develop, so that any diarrhea should be investigated thoroughly even though we may feel it is a relatively simple condition. The first intimation of amebae being associated with dysentery was made by Lösch in 1875, but because similar organisms were found in healthy individuals and in other conditions associated with diarrhea, it was not taken seriously. Later investigators noted the association regularly and also found the organisms at postmortem in the ulcerative lesions in the mucous membrane of the gut. Then Schaudinn suggested the presence of 2 distinct organisms of similar morphology, both parasitic, but one (*Endamoeba coli*) nonpathogenic, the other (*Endamoeba histolytica*) pathogenic and the cause of the condition known as amebic dysentery. For the purpose of this clinic and of practical medicine we may only mention in passing the other endameba found in bowel movements and the types that grow freely in bowel movements, ice cream and simple media, which are not a cause of serious pathology.

It is readily seen then that a diagnosis of endamebic dys-



entery must rest, as in our case, on two important factors, first the clinical story which may be that of acute attacks of diarrhea or mild attacks which are not severe enough to keep the patient from his work but which recur or persist for a few weeks and then clear up without definite treatment. Regularly, the colon is spastic and tender to pressure; cramplike pain may be severe with relief by passing gas and by bowel movements; temperature moderately raised, appetite lessened and nausea present, as might be seen in a simple diarrhea. During the intermittent stage the patient may feel normal. In severe or complicated cases symptoms are varied by the complications present as liver abscess, etc.; on examination of the bowel movement usually one finds fecal material mixed with mucus, pus and blood (not the watery secretion found in bacillary dysentery). In this mucous and bloody material the active organisms are found. Fresh warm specimens give best results, though specimens which are kept cold and warmed just before examination are very satisfactory as the organisms become active on warming. It is to be noted that in specimens kept at body temperature the organisms deteriorate rapidly so that they are not visible. Specimens for examination for the trophozoites may be mounted in saline solution or a dilute aqueous solution of eosin so that the organism will appear white on a pink background. The movement is sluglike, likely to be fairly active, red cells are ingested and the nucleus almost invisible unless stained in some way. If direct examination does not show organisms, saline cathartics may be given or material may be secured directly from the ulcers by rectal tube or proctoscopic examination. Single examinations with negative findings do not rule out a positive diagnosis. The finding of other organisms in material from the ulcers is to be expected because in the gut wall there is regularly a secondary infection. This may be responsible for difficulty in diagnosis in some cases in which an ulcerative colitis (idiopathic) is diagnosed, yet the case improves on emetin or similar treatment. In looking for carriers one must find encysted forms, usually by staining methods. Culture methods are technically difficult as are the

complement fixation methods. Though both may be of value if done by experts, neither is practical for a physician.

The life cycle of the *Endamoeba histolytica* is simple, consisting of two stages, first the trophozoites or motile forms which multiply rapidly in the large intestine producing the lesions and the symptoms of the disease. These motile forms are passed in large numbers but they die quickly when exposed to the air or stomach content and so do not transmit the disease. In the gut, conditions that are not compatible with growth of the trophozoites develop and they reproduce less rapidly and finally become encysted and are passed out of the bowel. These cysts when swallowed are broken up in the small intestine and a four-nucleated ameba is freed. These are held at points of stasis in the gut, divide into typical trophozoites and the usual lesions of amebic dysentery result. This makes the source of infection a carrier, who though passing cysts may be free from symptoms, perhaps may never have had enough diarrhea to fix it in his memory as being important, yet be the cause of epidemics as a handler of food, etc. The practical point is that any patient who has had amebic dysentery should be checked at regular intervals for months to be sure he is not a carrier.

The pathology of the disease is primarily that of the intestinal ulcers, commencing in the cecal region though the entire large gut may be involved; the lesions start as a small inflammatory area, surrounded by a hemorrhagic area. In the center necrosis of the epithelium takes place, into this the amebae pass destroying tissue, undermining the submucosa, giving an oval undermined erosion. Usually enough inflammatory reaction takes place so that perforation does not happen; between the ulcers are areas of fairly normal mucous membrane. As healing takes place, marked scar tissue develops which produces obstruction and, if the gut is pliable, dilatation above the point of obstruction. The organisms are found in the submucosa, in muscle layers and in small venules, in which they may be carried to the liver giving the complication of liver abscess. These abscesses are usually single, may be in any portion of the liver; occasionally there may be multiple abscesses or

numerous miliary lesions. Usually there is a destructive necrosis of liver tissue without liquefaction or marked inflammatory reaction in surrounding tissue. The lesion is walled off by granulation tissue and if secondary infection takes place, as it usually does, one gets the reactions due to the invading organisms, plus the findings of the amebae. These abscesses may be fairly quiescent for weeks, may gradually increase in size, may rupture into surrounding tissue, lung, pleura, peritoneum, or externally. If walled off and drained, they may heal readily. While liver abscess is noted as a part of the pathology and may be thought of as a complication, it must be remembered that intestinal ulcers followed by liver abscess normally indicate amebic infection. Liver abscess may be present without demonstrable lesions in the gut. Other pathology as complications include peritonitis from perforation or near perforation, appendiceal involvement, very infrequently urinary tract infection by transplanting or perforation, partial or complete intestinal obstruction. In all locations the ulcers are prone to become secondarily infected, giving a changed symptomatology and pathology and frequently increasing the danger to the patient. Certain authors go so far as to state that all ulcerative colitis is likely to have been primarily amebic, later being complicated by the secondary invading organisms. This gives the basis for anti-amebic treatment in all such cases with improvement resulting in a considerable number.

We began our history with the statement that our patient worked in the South and it is a fact that amebic dysentery is more common in tropical countries, not as an epidemic, but generally present. It is endemic in temperate zones, as our Chicago infection of a few years ago. Probably it is fair to say that we have cases quite regularly with us, that could be diagnosed if more frequent and careful microscopical examination of the bowel movements were made. Carriers, especially those who may handle food, vegetables that have been grown on ground fertilized by human excreta, contaminated water or milk supply, etc., must all be considered in the insidious extension of the disease. Careless laboratory technic is a possible

though probably not a frequent cause of infection. It is very difficult to establish an incubation period, inoculation experiments placing it at from thirty to one hundred days with the probability being that only a small percentage of people ingesting cysts actually develop amebic dysentery. Intestinal stasis and constipation on a basis of obstruction seem to increase the probability of pathology.

I am going to list definite cases in discussing the differential diagnosis, because in each the diagnosis of an amebic dysentery was considered during the course of the disease.

First, a twenty-five-year-old school teacher gave a history of acute and persisting diarrhea for several months, mucus and blood in the bowel movements, marked loss in weight, severe generalized abdominal cramps, and tenderness over the entire colon particularly in the right lower quadrant. At the time of examination her temperature was  $102^{\circ}$  to  $103^{\circ}$  F. in the afternoon. On fluoroscopic examination with a barium enema there was a definite filling defect in the cecum; the rest of the gut was spastic but not obstructed. No amebae were found on stool examination, nor were tubercle bacilli, though operation confirmed the probable diagnosis of tuberculosis.

The second patient was seen at the age of fifty years, with a history of cramplike pain in the lower abdomen, generalized but worse on the left side, frequent desire for bowel movements, 4 to 6 movements daily, with the passage of soft material frequently containing mucus and blood, and spastic and tender colon. The patient sat on the toilet to empty bladder because of the passage of bowel movement on straining. Appetite was diminished. He had slight nausea, but no vomiting, and had lost 10 pounds in weight. On examination temperature was  $98.6^{\circ}$  F., blood pressure 128/70, hemoglobin 90 per cent, and urine negative for sugar and albumin. Stomach secretions were normal and no blood was found. Bowel movements were mushy, with small amount of pus and persistent blood, but no amebae. Rectal examination revealed a small firm nodule, like a polyp, about 4 inches from the rectum. Fluoroscopic examination with barium enema showed partial obstruction in pelvic loop

of gut. The barium, however, passed in sufficient amount to fill the gut, showing no further filling defects. There was a definite delay in expelling the enema which caused the patient considerable distress. Proctoscopic examination revealed the polyp felt by rectal examination but could not reach the region of partial obstruction. A diagnosis of malignancy was made and operation advised. At surgery, resection revealed numerous flat polypi with broad bases; 2 large ones separated by a distance of 3 inches had undergone malignant degeneration, giving the findings of blood in the bowel movements. The mucous membrane between these lesions was normal. The patient has remained well following resection.

Third, a man, fifty-five years old, came in complaining of abdominal cramps for a period of three months, coming in attacks, associated with desire and straining at bowel movements. The material passed was mushy to watery in consistency. There was some rumbling, with relief of cramp by water enema; he sometimes used 2 to 4 enemas during twenty-four hours. Mucus was seen in the bowel movements and frequently there was a rather profuse amount of bright red blood. He had lost 10 pounds in weight but was working regularly.

On examination he weighed 144 $\frac{3}{4}$  pounds; temperature was 98.4° F. and blood pressure 150/104. Urine was negative for albumin and sugar. Hemoglobin 80 per cent. Ewald meal showed free acid 18, total 30, and negative benzidine test. Rectal examination was negative. The left side of the abdomen and the descending colon were tender to pressure. The first bowel movement examined was mushy in consistency, but negative to blood. A second series of bowel movements showed clots of blood, not digested, but no amebae. During hospital examination bowel movements at one time might be free from blood, but within an hour the patient would have a desire for movement and pass a large amount of fresh red blood, very definitely different from the usual occurrence in carcinoma, bleeding polyp, tuberculosis, or ulcerative colitis. Fluoroscopic examination with barium enema revealed a definite obstruction in the lower portion of the descending colon tight

enough so that only a small stream of barium would pass through. The enema caused a great deal of pain.

A diagnosis of malignancy was made, mention being made of the fact that certain of the bowel movements were free of blood which is not usual in a cancer of the colon, particularly the *descending portion*. At operation a palpable mass was felt at the location described; it was not hard, but the lumen of the gut was almost obstructed so resection was done. The mass was about 1 inch in diameter and cauliflower-like in appearance; on microscopic examination it was found to be a rare nodular hemangioma. The patient made an uneventful recovery following resection.

Other conditions which may give the same picture as the cases cited are infected diverticulitis, infected ulcerative polyp (nonmalignant), etc. Idiopathic ulcerative colitis furnishes the most difficult differentiation. The symptoms are more persistent and have all the earmarks of severe amebic dysentery. Except for the causative organisms, the clinical and laboratory findings are similar. One cannot be criticized too much for using anti-amebic medication in cases where the organism may not have been found, yet clinical or proctoscopic examination may be suggestive of amebic infection. Bacillary dysentery, food irritation, toxemias as from the thyroid or uremia, etc., also may be mentioned in connection with the differential diagnosis.

The treatment of amebic dysentery should take into consideration the entire clinical picture and should include the nourishment and general condition of the patient as well as the elimination of the causative organism. This means rest in bed, sufficient bland waste material, free food to provide nourishment, preparations of opium like deodorized tincture, 10 to 15 drops five times daily, paregoric, etc., to control the diarrhea. Bismuth preparations also help to control the diarrhea. As to specific treatment we have the arsenic preparations, such as stovarsol, in 3- or 4-grain doses three times a day for four to seven days, with a rest period of seven days and then resumption of treatment, treparsol, 5 grains, three times a day for

seven days with a seven-day rest period, yatren, 4 grains three times a day for seven to eight days, carbarsone, 4 grains twice daily for seven to ten days, and emetin which is given by intramuscular injection,  $\frac{1}{2}$  to 1 grain daily, for five to seven days, with a corresponding period without medication. With all arsenic preparations one must watch for symptoms of arsenic poisoning, and when noted promptly stop the drug, whatever it may be, until certain that the accumulative effect has had time to wear off. With emetin the toxic effect on the heart muscle is probably the greatest danger, making it a drug which requires greater attention even than the arsenic preparations.

I have been partial to stovarsol, as I used it early and find that if one watches for arsenic poisoning, it gives very satisfactory results. One must be cognizant of the fact that patients react differently; one patient may be influenced very little clinically or in the laboratory findings in the bowel movement by one drug, yet will get rapid clinical improvement and freedom from organisms from another type of medication. Each patient must be considered as an individual entity and clinical improvement, clearing of bowel movements from cysts and active organisms, and healing of ulcers must all result if treatment is satisfactory. Liver abscesses and other complications must be treated surgically as the condition demands, in addition to the regular medication outlined.

In the final analysis, one must remember and impress upon the patient that recurrences are frequent, to be expected, and dangerous, when present, to him as well as to his associates. This means repeated examinations and, if necessary, repeated and varied treatments with no immunity established from previous attacks.





## CLINIC OF DR. RALPH C. BROWN

### PRESBYTERIAN HOSPITAL

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#### DIAGNOSIS AND TREATMENT OF DUODENAL STASIS

DUODENAL stasis may arise from a wide range of pathological processes causing obstruction of the duodenum in any of its four anatomical portions. Thus, duodenal ulcer, carcinoma of the papilla of Vater, compression of the duodenum by a diseased gallbladder, adhesive bands constricting the duodenum, and carcinoma of the head of the pancreas, may be noted as not infrequent causes. I shall confine the discussion at this time, however, to the type of chronic duodenal stasis caused by arteriomesenteric compression of the third portion of the duodenum.

The interesting problems involved in the general subject of chronic duodenal stasis cannot be approached with clearness of understanding without brief reference to that relatively recent period in our morphological evolution in which the progenitors of men were four-footed animals, for in the four-footed animals the entire duodenum is a free intraperitoneal loop, with a mesentery hanging freely down in a vertical plane. When our forbears reared up on their hind legs and began to walk like man, there took place a marked change in the anatomical relationships of the bowel, and especially of the duodenum. The mesoduodenum disappeared, the duodenum posteriorly was deprived of much of its peritoneum, and as a result of the upright posture and rotation of the large bowel around the root of the mesentery, we find in man the *third* portion of the duodenum lodged in the acute angle between the spine and the root of the mesentery.

During the last decade of the last century, Dr. Lewis

Dwight, Professor of Anatomy at Harvard University, carried on an intensive study of variations in the anatomical relationships of the third portion of the duodenum, making wax casts in situ in 54 cadavers. These casts of the bowel showed varying degrees of compression of the duodenum in its third portion, as evidenced by indentations produced posteriorly by the spine and anteriorly by the root of the mesentery and the mesenteric artery. Thus it may be readily understood that the duodenum, placed as to its third portion in so precarious a position, may be compressed to a degree giving rise to obstructive symptoms as a result of any factor causing an increased drag on the root of the mesentery, especially when associated with lordosis of the spine.

Obstruction of the duodenum by this mechanism was recognized by Rokitansky in 1848. Excellent reviews of the literature with a series of case histories have been published by Kellogg, Higgins, and others. In the 1933 volume of the Transactions of the American Surgical Association may be found a thoroughly sound exposition of the subject by Eugene Pool, Walter Niles, and Kirby Martin. However, careful reading of the case histories recorded by these various writers shows a rather wide and variable range of symptoms resulting from duodenal stasis caused by arteriomesenteric obstruction. The diagnosis can be established with certainty only on the basis of careful roentgenologic observations, and later I shall emphasize the fact that minor degrees of lagging of barium in the second and third portions of the duodenum are all too frequently interpreted as the basis for variable local and general subjective symptoms which a more conservative viewpoint might consider due to causes other than chronic duodenal stasis. In none of these protocols was I able to find a symptom picture showing so clearly the widely intermittent, acute paroxysmal type of attacks suffered by the first 2 cases I shall describe.

The first case is that of a physician, age forty-three. For no less than twenty years he had had attacks of agonizing abdominal pain associated with the most intense nausea and

vomiting, each attack lasting from three to five days, the attacks occurring on an average of three to five times yearly. Between attacks he enjoyed a normal digestive function with freedom from abdominal distress. The onset of attacks occurred suddenly without warning symptoms, frequently awaking him from sound sleep. The initial symptoms were nausea and vomiting, immediately followed by severe, rhythmically recurring paroxysms of "tearing" pain, centered just to the right of the umbilicus and radiating to the lumbar region bilaterally. The pain was severe enough to produce profuse perspiration and render him oblivious to his surroundings. After protracted retching and vomiting some temporary relief from pain might be had, but within a brief time there would be recurrence of intense nausea, vomiting, and rhythmic type of pain. The vomitus at onset was fluid in character, containing mucus and bile. Upon two occasions the vomitus contained food eaten twenty-four hours previously. During attacks everything ingested would be immediately vomited, hence as the attacks progressed through three to five days continuously day and night, a marked degree of dehydration and profound prostration occurred with great loss of weight. The attacks ended abruptly and within a few hours normal ingestion of food and fluid could be resumed. It should be noted that the patient had no headache, which Dr. Crile considers a symptom of so much importance in his group of chronic duodenal stasis cases. Over a period of twenty years this physician had had scores of attacks of the character described, and the similarity between this clinical picture and that of the gastric crises of tabes dorsalis requires no comment. Physical examination, however, was negative with the exception of emaciation, and syphilis was excluded in so far as possible by serological tests and careful neurological examination.

Fluoroscopic examination in this case revealed normal filling of a moderately dilated stomach showing a marked degree of hyperperistalsis. Barium immediately passed on into the duodenum, the cap (showing no defect in contour) and the second portion of the duodenum filling to very large size, the

dilatation extending throughout the entire second portion. In spite of very vigorous peristalsis and an equally marked anti-peristalsis throughout the extent of this greatly dilated duodenum, a very long delay occurred before any barium passed on into the jejunum and long after barium had entirely left the stomach, a large pool of barium showing a fluid level remained in the dependent part of the second portion of the duodenum. Films show the size of this dilated duodenum to be approximately one third that of the moderately dilated stomach. A diagnosis of duodenojejunal angle obstruction was made and the abdomen was explored by a distinguished surgeon. Finding nothing in the region of the angulation other than the fact that the duodenum was fixed firmly to the abdominal wall by a very short ligament of Treitz, the abdomen was closed after removing the appendix. Two years later the patient returned with a continuation of the same distressing symptoms and as x-ray examination disclosed the same striking evidence of arteriomesenteric duodenal obstruction, a duodenojejunostomy was immediately performed with subsequent complete relief of symptoms during the period of years which has intervened. Fluoroscopic studies made after operation showed normal emptying time of the stomach and duodenum.

The second case is that of a young man of twenty-five, who had had paroxysmal attacks of epigastric pain associated with nausea and vomiting for ten years. The attacks would last two to three days, occurring about a year apart, but for the last three years the recurrent attacks had had a duration of about two weeks. The attacks would come on suddenly with severe pain and cramps in the epigastrium, rapidly spreading to the entire abdomen. The pain would double him up and during an attack he could not bear to have the abdomen touched. There would be profuse perspiration and a temperature rise to 102° F. and even to 104° F. He was often given hypodermics of morphine for relief, always losing a great deal of weight during the attacks and feeling weak for a long time after recovery. He had consulted many physicians and the diagnosis commonly made was that of gastritis or appendicitis. He was

of robust type, his normal weight being 180 pounds, was married and had two healthy children.

This patient entered the hospital on my service as an emergency case, having been suddenly seized with very severe epigastric pain a few hours before admission, associated with the most intense nausea and vomiting. Examination revealed some rigidity in the upper abdomen, no distention, temperature normal, urine normal, leukocytes 20,000. He was doubled up with pain and required morphine. A tumefaction in the right rectus region was seen with visible duodenal peristalsis from right to left. The second day temperature rose to 100° F. and the third day to 102° F. Pain, vomiting, fever, and high leukocytosis continued into the fourth day. Blood chlorides dropped to 300 mg. and the clinical picture was that of an acute surgical abdomen due to high intestinal obstruction.

**x-Ray Findings.**—Marked dilatation of second portion of the duodenum with delay in passage of barium into jejunum. A diagnosis of duodenojejunal angle obstruction was made, and twelve days after admission laparotomy showed great dilatation of the duodenum up to the root of the mesentery, but no other pathology with the exception of a slight, recent plastic exudate about the duodenojejunal fossa. An anastomosis between the dilated duodenum and the jejunum was made with uneventful recovery and complete relief from symptoms. Within six weeks the patient had regained the 25 pounds which had recently been lost. Here again we find a clinical picture of clearly intermittent, acute paroxysmal attacks, occurring very many times over a long period of years, causing the patient to be desperately ill for several days, with normal digestion between attacks. There can be no reason to doubt that in this, as in the preceding case, the obstructing factor was arteriomesenteric occlusion of the third portion of the duodenum. It is interesting to speculate on the mechanism involved. The second case had a history of troublesome constipation. It seems not unlikely that an overloaded colon may have intermittently caused just enough increased traction on the mesenteric root to precipitate the recurrent attacks of duo-

denal occlusion. It should again be noted that headache was not a part of the clinical picture.

The third case may throw light on the possible influence of two other factors in the causation of arteriomesenteric occlusion and immense dilatation of the duodenum, *i. e.*, emaciation and disturbance of the nerve supply to the duodenum causing atony. The patient was a man, thirty-nine years of age, seen in consultation at the Presbyterian Hospital. Four years earlier gallstones had been removed and the duodenum reported normal. Four months before my observation of the case a highly toxic goiter had been diagnosed and ligation of the vessels carried out with no improvement. Weight was rapidly lost and two weeks after ligation of the thyroid vessels he began having attacks of abdominal pain and vomiting, which became progressively more frequent and severe until his condition became desperate. His weight dropped from 125 to 91 pounds, he became delirious, dehydrated, profoundly toxic, and greatly emaciated. Visible gastric peristalsis appeared, suggesting duodenal obstruction.  $\alpha$ -Ray examination showed an enormously dilated stomach, a distended duodenal cap, and a really colossal degree of dilatation of the second portion of the duodenum. Several minutes elapsed before any barium passed the duodenojejunal flexure. The films of this case show a duodenal shadow approximately the size of a normal stomach. Five weeks later a successful duodenojejunostomy resulted in such great improvement that thyroidectomy could be safely done and the patient made a rapid and complete recovery. In this case it is probable that the emaciation and high degree of thyrotoxicosis (B.M.R. readings ranged from +55 to +59) were direct predisposing causes of the duodenal ileus, possibly through the mechanical effect of the loss of fat, but more probably through a profound dysfunction of the nerve supply to the duodenum causing atony.

Our interest in chronic duodenal stasis stimulated by these observations, we have sought for years for a clear-cut clinical picture resulting from lesser degrees of arteriomesenteric obstruction than were present in the 3 cases just

described. The net result of this study is an increasing degree of conservatism as to the indications for operation in what may be described as the borderline group of cases, individuals with chronic dyspepsia, absence of demonstrable pathology, and a duodenum which under fluoroscopic study shows some degree of dilatation of the second portion with reverse peristalsis and some cradling of barium. The following cases will serve to illustrate the point.

An able business executive, thirty-five years of age, had for fifteen years frequently recurring attacks of burning distress in the epigastrium with associated waves of nausea. Appendectomy had been done without relief. The symptoms were aggravated to a striking degree by fatigue and nervous strain. With the passing of years of poor health repeated and detailed medical examinations were made, with no evidence of pathology of gallbladder or peptic-ulcer type. A period of rigid ulcer treatment failed to give relief. Frequently he would be awakened at night with burning epigastric distress. He had no headaches. Attention was finally drawn to the fluoroscopic observation that with a large, well-filled duodenal cap the second portion of the duodenum filled to large size, with reverse peristalsis and some delay in the passage of barium into the jejunum. During fluoroscopic examination cramplike pain occurred at the time of the most active reverse peristalsis. Based upon this evidence the abdomen was explored, sharp angulation at the duodenojejunal flexure was found with dilatation and hypertrophy of the duodenum. Duodenojejunostomy was done and thereafter the patient had an appreciable degree of relief from dyspepsia. However, complete digestive health and comfort is enjoyed by this patient only when his constitutionally below par vegetative nervous system is freed from the effects of nervous stress and strain.

A young man, twenty-five years of age, came complaining of a similar epigastric burning distress of six years' duration, the symptoms being quite intermittent during the first four years. During the past two years, however, epigastric dis-

stress has been of daily occurrence. The relation to food-taking is similar to that of peptic ulcer and he gains relief by taking alkalis. Some associated pyrosis and vomiting and a great deal of night pain. No headaches. Previous history negative. Examination showed an individual of normal state of nutrition, normal blood pressure and blood findings. The secretory and motor functions of the stomach were normal. x-Ray examination showed what was reported to be a deformed duodenal cap, whereupon a diagnosis of duodenal ulcer was made and he gained temporary relief for some months on ulcer management, but eighteen months later he returned with the same symptoms. At that time visible gastric peristalsis indicated some degree of duodenal obstruction and fluoroscopic examination showed a normal duodenal cap, but the second portion of the duodenum filled to very large size with reverse peristalsis and delay in barium passing on into the jejunum. Upon opening the abdomen a band of adhesions was found stretched across the duodenal cap, and there were some adhesions about an apparently normal gall-bladder, but no evidence of peptic ulcer or ulcer scars, nor could any pathology be found at the duodenojejunal angle. Diagnosis, arteriomesenteric obstruction. A duodenojejunostomy was performed with complete recovery of excellent health.

Illustrating the type of case in which operation may do more harm than good, however, is the following: a spinster, thirty-seven years of age, a constitutionally below par type, fatiguing readily, with precordial pain, dyspnea on moderate exertion and right abdominal pain of many years' duration, associated with borborygmi and prodigious eructations. As is unfortunately true of so many chronic dyspeptics, she had had many operations; appendectomy, hysterectomy, an operation for adhesions, and an exploratory operation. Finally her condition was considered so unsatisfactory that upon finding x-ray evidence of a certain degree of duodenal stasis, she was again laparotomized. The second portion of the duodenum was found to be moderately enlarged and duodenojejunostomy



was performed. This was followed by several subsequent admissions on account of continuation of abdominal pain, nausea, fatigability, and other evidence of vegetative nervous system imbalance. Certainly no appreciable benefit could be credited to the various operative procedures, including the relief of what was believed to be a definite duodenal stasis. It is highly probable that the duodenal stasis in this case was a direct result of the below par state of the vegetative nervous system combined with loss of weight and that it had nothing to do with the initiation of her dyspeptic symptoms.

A similar case is that of an undernourished young society girl of nineteen, with a familial type of below par vegetative nervous system, her father being a severe migrainic. The symptom picture was one of dull epigastric pain after eating, anorexia, a spastic bowel, cold moist hands, marked fatigability, and headaches of marked migraine type.

On physical examination nothing abnormal could be found, but fluoroscopic examination disclosed a moderate degree of dilatation of the second portion of the duodenum with reverse peristalsis and lagging of barium. A very able internist advised that duodenojejunostomy be done. However, a period of bed rest in seclusion, with a high calorie diet and ample sleep cleared up the dyspepsia within a few weeks, and today, five years later, this young woman is in good health.

I believe there are many individuals with chronic dyspepsia and below par vegetative nervous system who may show from time to time such fluoroscopic findings of moderate dilatation of the duodenum, a little reverse peristalsis and possibly some lagging of barium. A great deal of conservatism should be exercised with relation to the operative treatment of this group of cases.

I wish strongly to emphasize the relatively insignificant amount of headache in the cases of genuine duodenal stasis on an arteriomesenteric basis that have come under our observation. Dr. Crile has reported good results from duodenojejunostomy in migraine sufferers having duodenal stasis, but until we possess more specific knowledge of the essential

nature of migraine, it would seem that this operative procedure should be resorted to only in cases where the x-ray findings permit of no doubt as to the existence of definite duodenal obstruction. Moderate increase in the circumference of the second portion of the duodenum with reverse peristalsis and cradling of barium may frequently be observed in normal individuals, hence the need for careful diagnostic study in the borderline cases before advising surgical operation.

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### THE PSEUDO-ULCER SYNDROME

It is common experience that the so-called "neurotic personality" who so frequently expresses his inadequacy by a "flight into illness" reaction, presents symptoms referable to the gastro-intestinal tract. The most common symptoms complained of by this type of individual are vaguely described by him as "stomach trouble." Indefinite epigastric distress, such as bloating, an uncomfortable sensation of fullness, particularly after eating, sensations often called by the patient "pain" but on direct questioning rarely found to be true painful sensations, are usually the most prominent complaints. Occasionally nausea and vomiting may occur. Not infrequently this type of patient who experiences some degree of nausea induces the vomiting by insertion of a finger into the pharynx. On rare occasions, as a result of severe retching, fresh blood may appear in the vomitus giving rise to exaggerated alarm on the part of the patient, and may cause the examiner to consider seriously the possibility of a definite peptic ulcer. The neurotic patient suffers commonly from constipation and is often an habitual user of laxatives. Sometimes diarrhea occurs, often of the "mucous colitis" type, a popular fad of a few decades ago. Such signs and symptoms may be considered as "pseudo-ulcer" syndrome.

While the existence of such an entity has been questioned by some, it seems quite definite that there are a certain number of patients presenting a second type of "pseudo-ulcer" with characteristic subjective manifestations typical of peptic

ulcer, in whom repeated careful roentgenologic and laboratory studies fail to reveal any positive objective findings. The latter group has the perfect foundation for ulcer, but the "gastric defense mechanism"<sup>1</sup> is able to meet the situation despite pylorospasm and "ulcer" distress. The patient has all the symptoms, but no ulcer. The first group also move into the second group after they have better learned the proper symptoms of ulcer from doctors, newspapers, ulcer-bearing friends, and drug store pamphlets. The first group more properly would fall into the general group loosely called "nervous indigestion." When the pseudo-ulcer patient is "pressed" too hard by environment, overly fatigued, exposed to infection, or forced to eat a very irritating diet, he may eventually develop an organic ulcer.

Eusterman and Balfour<sup>2</sup> have tabulated the results of statistical studies by Blackford,<sup>3</sup> Foster,<sup>4</sup> Davis and Vander Hoof,<sup>5</sup> indicating the frequency of the various causes of dyspepsia encountered in hospitals and private practice. Their figures, representing a total of 7300 cases with symptoms of gastric disturbance, indicate that purely functional causes are responsible for 22 to 25 per cent of the complaints. Actual organic disease of the stomach or duodenum accounted for approximately 14 per cent.

A more recent study by Dwyer and Blackford<sup>6</sup> tabulating the results of a study of 3000 cases, showed that organic conditions of the stomach or duodenum were found in only 15 per cent of the cases. Reflex disturbance resulting from gall-bladder pathology was found to be the most frequent organic cause of indigestion.

In a consecutive series of 15,000 patients with chronic dyspepsia examined at the Mayo Clinic, Alvarez<sup>7</sup> reports that a total of only 18 per cent of patients' digestive disturbances were the result of organic disease of the stomach or duodenum.

It is evident, therefore, that from the standpoint of both diagnosis and therapy, only a relatively small percentage of patients with chronic dyspepsia have organic changes of the

stomach and duodenum. Some 60 per cent can be accounted for on the basis of reflex disturbance resulting from pathology elsewhere in the gastro-intestinal tract or gallbladder. Approximately 25 per cent fall into the functional group and may or may not present the "pseudo-ulcer" syndrome.

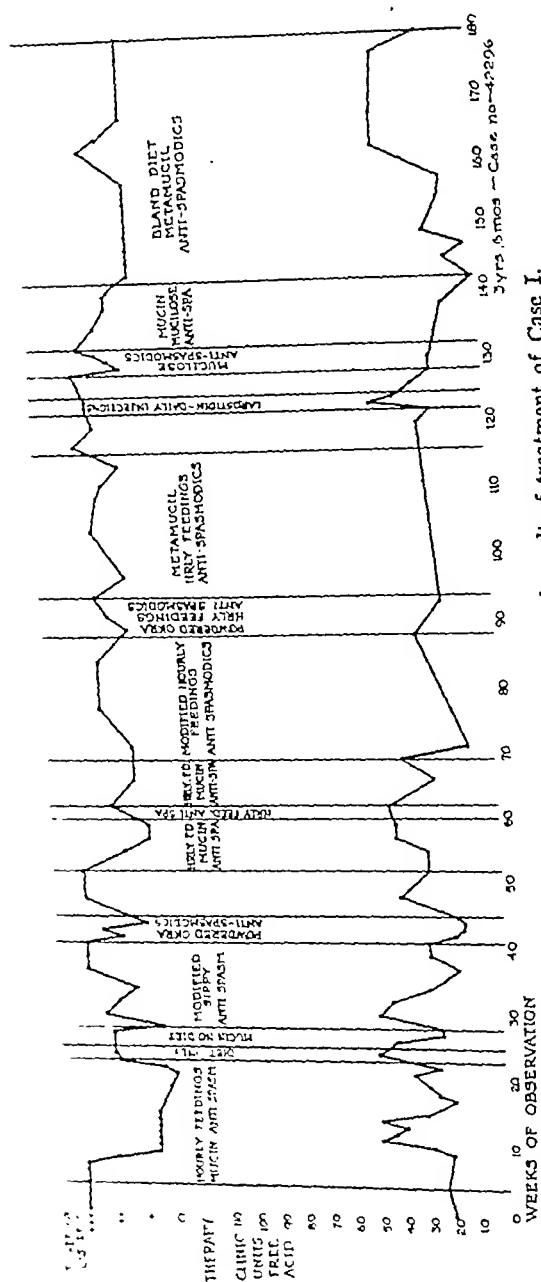
Before diagnosing a case of "chronic dyspepsia" as of functional origin in this or any other clinic, it is paramount that all possible organic causes, reflex or otherwise, be definitely ruled out. Careful objective study of the gallbladder, appendix, and entire gastro-intestinal tract are essential. In too many instances the patient is either diagnosed as having a peptic ulcer without objective evidence, or unwarrantedly declared to be just "another extremely nervous individual."

At best, the symptomatology of pseudo-ulcer is extremely variable. Vague, dull, aching pain in the epigastrium, poorly localized, usually brought on by emotional stress and strain, an irregular relationship to the intake of food, and not relieved by ordinary medical measures successful in the treatment of true peptic ulcer, is the characteristic history. Associated signs and symptoms may or may not be present. In some cases, there is nausea and vomiting. (Perhaps since the widespread use of the gastroscope there may be a tendency to call this picture by its old all-embracing name, "gastritis.") Localized tenderness is usually absent on palpation of the epigastrium, a finding which occasionally tends to differentiate the condition from true ulcer. During periods in which the patient is free from emotional strain, he is liable to forget all about previous gastric complaints, exaggerating excellent health until he is confronted again by an emotional or psychological problem, the solution of which he finds too difficult. As a result, he again resorts to the "flight into illness" reaction, as expressed by his gastro-intestinal symptoms. Examination of the patient rarely reveals any definite findings. The patient may show exaggerated reactions to abdominal palpation, displaying anxiety and fear.

The patients whom we present to you today are typical of the first type of functional "dyspepsia," in whom the

symptom complex somewhat simulates that of peptic ulcer. Four out of the 5 have been diagnosed as peptic ulcer patients at other institutions.

**Case I.**—S. B., a white male, aged thirty-two years, was admitted to the St. Luke's Hospital Out-patient Department on December 2, 1931, complaining of a heavy feeling in the epigastrium occurring periodically for two and one-half years, 40 pounds' loss in weight over this period, belching, and constipation. There was also a sensation of diffuse abdominal discomfort of indefinite description. The epigastric discomfort was relieved by the taking of food, but only at times occurred with relation to meals. Cathartics were resorted to regularly in order to induce bowel movements. The remainder of the history and physical examination was negative. There were no positive laboratory findings. In general, however, the patient appeared weak and pale and seemed to appear to feel much worse than most ulcer patients. A tentative diagnosis of spastic colitis was made, and the patient was placed upon a bland diet, antispasmodics, and kept under observation. He ran an irregular course without much subjective or objective improvement, continued to lose weight, and was referred to our clinic August 17, 1932. Frequent aspirations and analyses of the stomach contents were begun at this time. The record of free hydrochloric acid values thus obtained may be seen in Fig. 11. A complete roentgenologic study of the gastro-intestinal tract revealed only a spastic duodenal bulb with no constant deformity. In view of all findings, this patient was studied as a non-ulcerbearing individual but was started upon gastric mucin, hourly feedings, antispasmodics, and subsequently received therapy similar in character to that prescribed for patients with peptic ulcer in this clinic. During our observation, the patient had remained approximately the same objectively, as indicated in the chart (Fig. 11). His epigastric discomfort has decreased markedly during the past year, and at present his chief complaint is constipation. This has been adequately controlled by metamucil. It is significant



that no duodenal deformity has been apparent in any of the  
 twenty rechecks. He has many of the proper symptoms, but

apparently cannot develop an ulcer. We consider such a patient as being a potential ulcer-bearing individual.

This illustrates how a patient who apparently had no peptic ulcer did not improve for years until the management included attention to the strong neurogenic and psychogenic factors. He was able to return to work and was one of our most grateful patients.

**Case II.**—L. A., a white male, aged forty-eight years, was admitted to the neurological service of St. Luke's Hospital May 25, 1933, complaining of dizziness and nervousness since the fall of 1932 following an appendectomy, the loss of a job he had had in a laundry for twenty-one years, and eviction from his house. The patient states that he was very depressed at the time, but felt somewhat better now. On questioning, the patient revealed that he was extremely unhappy at home, had a nagging wife, and that in the course of their frequent disputes, his sons would usually take her side. A diagnosis of psychoneurosis was made, and the patient was placed on sedative medication. On November 19, 1933, the patient was referred to our clinic complaining of dull headaches, a burning sensation in the epigastrium radiating to the neck, marked flatulence, constipation, hemorrhoids, dizziness, nervousness, shooting pains and weakness in the arms and legs, and in addition stated that he thought he was becoming impotent, that he might have a goiter, that he might have prostate trouble, and that he had no resistance to colds. The epigastric discomfort occurred anywhere from one-half to one hour after eating, and was sometimes accompanied by nausea and vomiting. He attributes the latter difficulty to his wife's poor cooking. By and large, his greatest complaint was his wife, whom he said was not affectionate and failed to understand him despite twenty years of married life. In 1923, the patient had a tonsillectomy and adenoidectomy, in 1930, gonorrhea, and in 1932, an appendectomy. Hourly feedings were prescribed and psychotherapy administered. On December 4, 1933, the patient was referred to neurology, and at



this time complained that his wife and two sons "had taken everything from him and treated him like a dog." He now had to eat cold cereal for breakfast because his wife refused to get up and cook for him. Following this meal he would usually retire to the outdoors to vomit it up. The patient stated that he had no desire to work, because if he earned any money, it would have to be used to pay rent for his wife. He further expressed the conviction that his gonorrheal infection in 1930 followed the return of his wife from a six months' trip to Michigan. The subsequent history consisted chiefly of accounts of his marital difficulties. On one occasion the patient presented himself at the clinic with a black and blue arm following an effort to guard himself when his wife tried to kick him in the testicles. Following this episode, the patient was advised to become a sailor but, as with other psychotherapy in this case, met with no success. Seventy gastric analyses during various types of management were obtained on this patient. The results showed an almost persistent hyperacidity. However, repeated roentgenologic examinations of the gastro-intestinal tract failed to reveal any pathology. When we recommended that the patient go to work, he demurred, became aggravated, and stopped attending our clinic.

**Case III.**—E. W., a white male, thirty-one years of age, was admitted to the St. Luke's Hospital Out-patient Department May 8, 1931, complaining of convulsive seizures of two years' duration, epigastric discomfort of seven months' duration, and the swelling of a gland in his neck of one week's duration. The patient stated that the epigastric discomfort occurred on the average of several times a month and would sometimes last as long as two hours. Usually the distress would start between one and two hours after meals. Frequently there was an accompanying nausea, but no vomiting. On physical examination the patient was found to have a slight fever, cervical lymphadenopathy, and a palpable thyroid. A diagnosis of infection of the right tonsillar stump was

made, and the patient was treated accordingly. He was subsequently referred to neurology where a diagnosis of idiopathic epilepsy was made. May 17, 1933, the patient was referred to our clinic. At this time, he complained of dull epigastric pain, continuous in nature, and unrelated to the taking of food. The patient further complained of belching, flatulence and constipation. Repeated gastric analyses revealed no positive information. The roentgenologic studies of the gastro-intestinal tract were likewise negative. The patient was placed on hourly feedings and antispasmodics, and obtained considerable relief. At the present time, the patient is on a bland dietary management in conjunction with antispasmodic medication. He is still subject to periodic recurrences of distress, at which time hourly feedings are again prescribed. This patient illustrates the typical "flight into illness" reaction and responds only to dietary and psychotherapeutic management.

**Case IV.**—N. L. J., a colored male, thirty years of age, was admitted to the St. Luke's Hospital Out-patient Department, January 27, 1929, complaining of epigastric distress, regurgitation of food after eating, and upper right quadrant pain referred to the right shoulder. The patient stated that he began to have "stomach trouble" about nine years ago and was treated at this time for a period of five weeks at a large Baltimore hospital. He was given powders and a liquid medicine, the exact nature of which he did not know. He never was entirely cured, and the distress recurred at intervals varying from one week to one month since that time. For the past four months, the pain has been present following every meal and has been extremely intense at night. Usually the distress begins as a heavy feeling in the region of the umbilicus, and then radiates to a small area in the epigastrium. It then travels to the right upper quadrant and finally to the right scapula. On some occasions the pain begins while the patient is eating, but usually starts between fifteen minutes and one hour after the meal. The patient states that the

distress has made him feel very nervous and that for the past three months he has been unable to work. For about two years he has regurgitated sour material after eating. In recent months he has been taking various powders and patent medicines, but has been unable to obtain relief. The physical examination of this patient was not significant. Blood Wassermann and Kahn tests were found positive, and the patient was placed on antiluetic therapy. A roentgenologic study of the gastro-intestinal tract revealed a highly spastic colon and a deformity of the duodenum which was not constant and interpreted as being a highly questionable duodenal ulcer. Sippy management was instituted, and only slight improvement was noted. Mucin therapy was tried in August, 1932, following which the patient began to show marked subjective relief. The right upper quadrant distress was relieved by keto-cholanic acid.\* The routine gastric analyses performed on this patient were not clearly indicative of organic pathology.

This patient definitely falls into that group in which there are not sufficient positive objective findings to make an out-and-out diagnosis of peptic ulcer. The history itself was atypical. The gastro-intestinal condition did not improve on antiluetic therapy. We feel that such a case comes under the pseudo-ulcer classification, and should be carefully watched, as well as being given ulcer therapy.

Case V.—J. B., a white male, forty-two years of age, was admitted to the St. Luke's Hospital Out-patient Department, December 28, 1932, complaining of dull epigastric pain, unrelated to the taking of food, pain in both lower quadrants, weakness, nervousness, and loose watery stools. The distress first began four years ago and has continued more or less regularly since that time. On physical examination the thyroid was found to be slightly enlarged but soft, the skin moist, and the reflexes hyperactive. There was a hypertension and tachycardia. A basal metabolism test was ordered, but was

\* Not available as yet

found to be within normal limits. A complete roentgenologic study of the gastro-intestinal tract revealed no pathology. Hourly feedings and antispasmodics were prescribed, but the patient still continued to have indefinite epigastric distress. In February, 1934, the patient stated that he had a sharp cramplike pain beginning in the epigastrium and localizing in the right lower quadrant. Physical examination revealed slight rigidity over McBurney's point, and this information, together with the finding of an elevation in the white blood count, indicated a diagnosis of appendicitis. An appendectomy was done, typical pathology found, and the patient made an uneventful recovery. The epigastric distress, however, continued. A second roentgenological study still failed to demonstrate any abnormal findings. Late in 1935, the patient underwent a period in which he had considerable marital and family difficulties in addition to financial worries. The epigastric distress increased in severity, and this time the roentgenologic study demonstrated a definitely deformed duodenal bulb. The patient is now on our routine ulcer management with animal mucin and metamucil, and is beginning to show marked improvement.

This patient apparently can be classified as an atypical "pseudo-ulcer" type of individual who finally developed an ulcer while under our observation.

#### DISCUSSION

Under our designation of "pseudo-ulcer" syndrome are to be found two main groups. The first may be considered "psychogenic," occurring in the familiar psychoneuroses. The second group we have designated "neurogenic," implying a more definite involvement of the physiology of the gastro-intestinal tract as a result of interference with the nervous mechanism as stated above. A sharp distinction cannot be made between these 2 groups in many instances, due to the fact that associated with the "psychogenic" gastro-intestinal disorders and attributable to the physiologic changes resulting from emotional factors, certain disturbances of gastro-intes-

tinal function actually occur. More typical of the neurogenic group are those instances of pseudo-ulcer syndrome which arise reflexly from pathologic conditions of neighboring organs. In this latter group, attention must be paid chiefly to these sources.

The physiologic alterations of the gastro-intestinal tract occurring as a result of abnormal emotional reactions must be properly emphasized. It is well known that the neurasthenic patient frequently may show spastic phenomena and hyperirritability of the gastro-intestinal tract. Therefore, although the basic cause of the patient's disturbance may be psychogenic, these bodily changes associated or arising secondarily, must be looked upon as physiologic problems, "neurogenic" in origin, and merit due consideration in the plan of therapy. Although psychotherapy should constitute the chief therapeutic procedure, this must be supplemented by the common sense use of dietary and medical measures commonly employed in the treatment of organic gastro-intestinal tract disease. Thus, frequent, small, bland feedings, with the judicious use of gastro-intestinal tract sedatives as indicated, have a definite place in the handling of such functional gastric disorders.

The "pseudo-ulcer" patient should be so managed as to enable him to overcome the neurogenic factors tending to produce peptic ulcer. His mode of living must be so altered as to shelter him from the difficult environmental stimuli received in every day life. With some private patients this may be accomplished by a vacation trip, but they must be prepared emotionally for return to their original environment. If the former course is impractical, as it was in our clinic patients, their attitudes must be so molded that they may adjust to the untoward situations occasioned by their anxiety. Stimuli related to poverty, starvation, insecurity, frequent evictions, etc., should be made to be ineffective except in so far as the patient is able to control the circumstances. The inadequate person oftentimes is not making all possible use of his available personality. With treatment a much more adequate "carefree" or anxiety-free personality may result.

A convenient point of view, easily grasped by the patient, is that one must recognize the fact that the world is normally the way it is—trouble, trial, lack of appreciation, meanness, cupidity, injustice, or ingratitude—all being attributes of human character. He should be made to appreciate that, after all, it is the only world we have. Encouragement, suggestion, reassurance, together with methods to overcome chronic fatigue, eventually change the visceral reflex threshold controlling pylorospasm, peristalsis, etc. It is generally agreed that many of the physiological changes are secondary to, or actually a part of, emotion, and the residual or more complicated histological changes are due to many repeated stimuli.

The success of such a method of treatment depends upon a favorable relationship between the patient and the doctor *i. e.*, transference. Talks with the patient are a possible means of giving him an insight into his maladjustment and effecting a possible change in his personality, enabling him to better meet the emotional problems. In some cases, simple methods do not suffice, and the patient is unimprovable. Such cases definitely require psychiatric consultation. Above all, the patient should never be told "not to worry." Such advice has probably been given by the patient's family and would-be friends for years before he sought medical attention. The patient should worry just enough to get along in the world and follow his management.

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## CLINIC OF DR. JESSE R. GERSTLEY

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### THE TREATMENT OF PNEUMONIA IN CHILDREN

THIS boy, aged ten years, has just recovered from one of the severest attacks of pneumonia I have ever seen. For a week before the onset he complained of being tired, languid and not feeling well. Being a child who adopted this ruse occasionally in order to avoid school, this aroused no particular concern. His parents noted that he looked well, that his morning and evening temperature were normal, and sent him protesting on his way. On the morning of December 1st, he awoke with a chill, vomiting, and fever of 103° F. He complained somewhat apathetically of headache and dizziness. Within a few hours the temperature rose to 106° F., and his pathetic, pinched face and dazed demeanor showed him to be the victim of a highly virulent infection. To quote his mother, "He's sicker than I have ever seen him. He's really sick this time."

The vomiting continued so perniciously during the day that not even a teaspoonful of water was retained.

The following morning found him slightly cyanotic, still vomiting and very toxic. Some impairment of resonance in the right lower lobe posteriorly, with a diminution of breath sounds, revealed the diagnosis. Accordingly he was rushed to the hospital and put in an oxygen tent.

On admission his temperature was 106.6° F., pulse 136, respiration 36; white blood count 23,000, with 85 per cent polymorphonuclears. He tended to be apathetic but was reasonably rational when aroused. His cough was not particularly troublesome. Other than the chest involvement and dilatation

of the wings of the nose on respiration, physical findings were negative.

Dilatation of the wings of the nose on respiration is one of the most valuable signs in the diagnosis of pneumonia in children. Many times the physical findings do not become manifest for some days and this sign furnishes the first valuable clue.

At times he complained of pain in the right lower abdomen. A scar, however, saved us the difficulty of ruling out appendicitis.

He was now so toxic from the combined effects of infection and dehydration that he was given an intravenous drip of 225 cc. of equal parts normal saline and 10 per cent glucose, followed in two hours by an additional 350 cc. of 10 per cent glucose. The fluid and carbohydrate temporarily diminished the toxicity and gratified his pathetic need of water.

On the afternoon of the third day he became intensely delirious. The oxygen tent filled him with wild fears, the noise of the motor terrified him, and he sat up and struggled frantically to escape. In desperation we took the tent away and quieted him with a hypodermic of  $\frac{1}{12}$  grain of morphine.

I consider morphine one of the most valuable drugs in such a crisis. No matter what one reads of its depressing effects, the first essential in the treatment of such a severe illness is quiet. In my experience morphine in doses small but enough to quiet the patient is invaluable, and really acts as a stimulant. Next to morphine ranks codeine in sufficient dosage.

Following the morphine he became much quieter, with a slight drop in temperature, pulse and respiration, but within a few hours the fever was back to 105° F. and he was complaining of pain in his left ear. There was some tenderness on pressure and the drum was dull and slightly bulging.

The fifth day in the hospital was a severe one. At the dreary hour of four in the morning when life forces are at their lowest, the little boy had a severe chill lasting about fifteen minutes, followed by cyanosis, thready pulse, marked restlessness and delirium, repeated emesis, and abdominal disten-



tion. Cough for the first time became distressing. He was replaced in the oxygen tent and given 2 grains of caffeine sodium benzoate hypodermically. In the afternoon with fever of  $106^{\circ}$  F. his condition seemed so critical that he was given a transfusion of 120 cc. of whole blood intravenously into the ankle vein, followed by an intravenous drip of 300 cc. of Hartmann's solution.

One of the most valuable advances in the treatment of any sepsis combined with dehydration and starvation has been the use of the intravenous drip, and this has been greatly facilitated by the technic devised by one of our former interns, Dr. M. L. Spivek.<sup>1</sup> Every one of you should make it a point to read the article and familiarize yourself with the technic.

A portable x-ray showed involvement of the entire right chest, the shadow being somewhat denser in the right upper lobe. Unquestionably the chill followed the involvement of this lobe. Whenever a chill occurs during the *course* of an acute infection in a child, look out for trouble. Examination showed bronchophony and bronchial breathing all through the upper part of the chest, anterior, posterior, and in the axilla.

On the morning of the sixth day at 4:30 the patient again suffered collapse, with temperature dropping to  $102^{\circ}$  F., cyanosis, chilly sensations, and a weak pulse. He complained of dyspnea and nausea. In the afternoon with temperature back at  $106^{\circ}$  F., rapid thready pulse, cyanosis, abdominal distention, and with vomiting still preventing any fluid retention, he was given another blood transfusion of 150 cc. into the ankle vein, followed by intravenous drip of 700 cc. of Hartmann's solution containing 50 cc. of 50 per cent glucose. Following this, the little boy became definitely better. The temperature, pulse and respiration remained unchanged, but his appearance was definitely less toxic. Two days later his temperature dropped to  $102.6^{\circ}$  F. but by afternoon it was back to  $104^{\circ}$  F.

Look out for these pseudo-crises! In the early days of my practice I used to be fooled by them. A patient is never

<sup>1</sup> See M. L. Spivek, Simple Method of Transfusion for Infants and Children, *Am. J. Surg.* 7, 1934 (August), 1935.

out of danger unless the temperature has dropped to subnormal. A drop to anywhere above normal may be of no significance. It may mean that the disease is going to terminate by lysis. But be on the alert for complications.

From this time with one exception there was continual improvement and the temperature dropped slowly by lysis to normal on the thirteenth day. With the steady improvement, the oxygen was reduced daily about 10 per cent, from 50 to 20, and he was taken from the tent.

You remember that on the fourth day he complained of pain in the ear, and examination showed some bulging of the drum. He was so desperately sick that I did not want to subject him to one bit of further strain. Anyway, I am perhaps ultraconservative as regards puncture of the ear drum in children. In my experience harm rarely results from waiting unless the condition is most acute. In this case the pain disappeared after a few hours. However, the findings remained and even after he became perfectly rational he seemed hard of hearing. At this time the ear was opened, the pus evacuated, and within three days this entire complication had cleared up. I am quite sure that it healed much more rapidly than it would have, had it not been handled so conservatively.

This case is of particular interest because it illustrates the type of disease confronting us at the present. It illustrates the insidious prodromes, the difficulty of an early diagnosis, and a common complication. It illustrates modern methods of treatment without which I believe we would have been unsuccessful.

In this clinic I am going to limit my discussion to that of treatment. I should like to speak of the various pathological, bacteriological, and clinical types of pneumonia; the onset often so insidious; the frequent difficulty of early diagnosis; the critical judgment and experience required at times to differentiate the early stages of the disease from appendicitis or to determine the onset of a complicating appendicitis or peritonitis, and the common complications such as otitis and empyema but time will not permit.

## TREATMENT

**Prophylaxis.**—Is there a prophylactic treatment? There is no question that since the World War the common type of pneumonia has changed. No matter what the organism, the clinical course, especially in the treacherous and insidious onset, smacks of influenza. You usually get a history of a mild fever for a day or two, then a day of normal temperature. The mother or inexperienced physician reassured by the absence of fever relaxes vigilance. Then on the third or fourth day comes a dramatic recrudescence and the patient has pneumonia. Such is usually called a relapse. I am inclined to think it is the normal picture and that during the present years these mild upper respiratory infections should be treated as if the ordinary course of the infection were a day or two of fever, a day of normal temperature, and a day of recurrence of fever. It is just here that we must practice our prophylaxis.

Whenever there is much pneumonia around, watch out for this first day of normal temperature and don't relax your vigilance until the one day has been extended to two. I tell parents that during the first day of normal temperature they should observe precautions identical to those used during the time of acute illness. This means absolute rest in bed, no excitement, no visitors, and a light diet. If available, a bedpan should be used, and if this is impossible the child should be carried to the toilet, and before being taken from bed should be dressed in stockings, slippers and a robe to avoid chilling. By this procedure I have relieved myself of qualms of conscience that used to come at the beginning of this period of new experience, when the prodromal symptoms were overlooked.

**Active Treatment.**—In discussing the treatment of pneumonia I will first discuss the conventional treatment, and then discuss the special procedures which I think were responsible for saving the boy's life.

**Rest.**—Once the disease has been recognized, the all-important treatment is *rest*. I cannot emphasize this too strongly. And when I say *rest*, I do not mean rest conversationally or rest on the patient's record, but *complete physical and mental*

*rest for the patient.* Far more patients are lost by too much rather than too little treatment. Certainly every case does not need hospital care. One must always balance the disadvantage of moving a patient from his home, with the advantages of hospital facilities. I rarely advise hospitalization unless there is a very definite indication.

**Nursing.**—Pneumonia is still a disease in which the basic treatment is one of nursing. The nurse must be instructed to be quiet, unobtrusive, and to disturb the patient as little as possible. Many nurses are overzealous in their efforts to keep the bed in order, to keep the patient clean, and to wear him out with a toothbrush. The physician must watch the nurse carefully in all such details. The nurse should permit no visitors, and should make every effort to keep parents and relatives out of the sick room. Needless to say, the room should be well ventilated and this must be done even at the expense of the nurse's comfort. While the decade is over where we advocate unusually low temperatures, there is no question but that the patient is more comfortable in a moderately cool room.

**Fever.**—We are not as concerned about fever as we used to be. For a temperature over 103° F. I usually order small doses of acetylsalicylic acid from 1 grain in an infant to 5 grains in a child of six or over. A cool cloth to the head and a tepid sponge may make the patient decidedly more comfortable, but in giving the sponge do not overdo it; be careful that your little patient is not exposed to any possible chilling. The *priessnitz* (a wet cloth wrapped around the chest and enclosed in oiled silk) may quiet a delirious patient. It must be kept moist, however, or it becomes an extra blanket. The added weight to the chest also may oppress the patient. In this respect let me speak of my particular hobby, now a protest of twenty years' duration, against the universal practice of pinning the infant's shirt to the diaper. Just at the time when the child is using every thoracic and abdominal muscle in his struggle against asphyxia, any additional handicap to these muscles may turn the tide.

In former years a temperature of 105° F. was considered

an absolute indication for vigorous treatment. I do not think this holds true in a child. Indeed, I have entirely changed my tactics, and at these extreme temperatures rather fear the active hydrotherapeutic procedures. At 106° F. the child may complain of being chilly; the extremities cold. Under such circumstances the cold sponge may do more harm than good, particularly following a chill. A cloth wrung out in warm water and applied to the chest and hot water bags to the feet, may be more advantageous than cold applications.

Perhaps the best therapy for fever is after all giving the patient plenty of fluid, so that he has an abundant supply to drain the heat from his body through perspiration and respiration.

**Acidosis.**—This is recognized by finding acetone in the urine. Some men give various alkalis. The most effective therapy is plenty of carbohydrate and Hartmann's solution, intravenously if necessary.

**Tympanites.**—Tympanites in itself is a grave sign. It is a manifestation of toxic ileus. By pressing upward on the diaphragm it decreases the available air space in the thorax and presents an additional handicap to the patient. One may reduce tympanites by mild cathartics, such as magnesium citrate or milk of magnesia. As a rule, I find cathartics are only of temporary assistance and sometimes seem to be followed by increased distention. They also tend to upset the stomach. Equally satisfactory results can be obtained by a simple glycerin suppository or better yet, by the 1-2-3 enema, consisting of 1 ounce of glycerin, 2 ounces of magnesium sulphate and 3 ounces of water. Pituitrin may be of value, and at times I have thought that I obtained results by injecting from  $\frac{1}{2}$  to 1 ampule of pituitrin into the abdominal cavity.

When tympanites is present, milk sometimes increases the discomfort. The digestion of milk is facilitated by peptonization, the addition of acid, or dilution with carbonated water. However, when there is much abdominal distention I prefer as little milk as possible. Weak tea or fruit juices do better.

The patient may also be made somewhat more comfortable

by propping him up. Here the thoracic viscera help weigh the diaphragm down and to some extent combat the upward pressure from the abdomen.

**Specific Therapy.**—The drug, optochin, which was introduced as a specific has, as far as I know, not lived up to the original claim. I have had little experience with it, and believe it is considered dangerous by some. There are, of course, various sera to be obtained and in desperate cases one may resort to these. Certainly favorable results have followed the use of Type I antipneumococcus serum, and the concentrated serum of Felton. I have had little experience with these because my recent interest has been in convalescent serum.

**Stimulation.**—It has always seemed to me that adrenalin given hypodermically in doses of 2 to 5 minims is the most effective drug in maintaining blood pressure. I usually combine it with camphor and oil which is a good emergency stimulant. Some men have gone back to strychnine, while caffeine sodium benzoate is again returning to vogue. I have recently come to have more confidence in blood transfusion than in any medication for the support of failing circulation and blood pressure.

**Diet.**—By careful supervision of the diet we certainly can facilitate the ultimate recovery of the patient. The indications to be met are:

(a) The diet must facilitate recovery from the initial vomiting, and protect against further gastro-intestinal disturbance.

(b) Following cessation of the vomiting the diet must contain sufficient fluid.

(c) It must contain nutriment, especially carbohydrate. The latter is of particular value in sustaining the circulation and in overcoming acidosis.

(d) As soon as possible the diet must contain increasing caloric and nutritive elements.

**First Day.**—For the first twenty-four hours it is safer to give the patient nothing but hot weak tea, with sugar and lemon. I prefer no milk. If the vomiting ceases, the child may also have a little water and some hot clear soup. It is

always more advisable to offer small quantities of fluid frequently repeated. Larger amounts tend to nausea and by overloading the stomach interfere with respiration.

*Second Day.*—As soon as feasible we meet two indications: maintaining body fluid and supplying sufficient carbohydrate to sustain the circulation.

I think we have been remiss in estimating the amount of fluid required during an acute illness. This youngster after the first day in the hospital (during which he took only 9 ounces) took 2 quarts daily during most of the acute stage in addition to the blood and saline transfusions. Whether a child is receiving sufficient fluid is indicated by the specific gravity of the urine.

Vomiting having ceased, one might offer increased quantities of fluid; water, orangeade, lemonade, iced tea, ice pellets, ices, fruit juices; and even nutriment as milk, and possibly small quantities of malted milk, cereal, jello, custard, ice cream, toast, cracker and baked potato.

The advantages of ice pellets and ices are that though taken in small quantities they tend to lower the temperature.

In an infant the formula, and in an older child the first whole milk feeding should be diluted. Equal parts whole milk and carbonated water make a pleasant beverage for a child of over a year.

Any cereal may be used depending upon the child's habit and taste. Pabulum of Mead Johnson and Company may be the most easily digested. I prefer it prepared with water rather than milk during the height of the illness, and add only half milk instead of whole milk on the first serving. Of course if the attack is at all severe, the patient should take nothing but fluids for several days.

Carbohydrate in adequate amount is life-saving. It is both a food and a circulatory stimulant. It is urgently demanded when acetone is found in the urine. It can be given as sucrose, lactose, glucose, or the malt and dextrin preparations. The maximum quantity should be added to all food and liquid without interfering with the taste. I like sucrose the least

because it is sweetest. Lactose or the more soluble beta-lactose has the advantage of being less sweet and of favoring a gram-positive flora which is not gas-producing. Glucose is sweeter but requires no digestion. In every case the problem is individual and the child should be offered the carbohydrate of which he takes the most. The fruit juices are often the best vehicles; grapefruit juice is especially advantageous. Children usually will not tolerate carbohydrate in water or milk, while they will in tea. Under no circumstances should a basic essential food be tampered with in a way to make it unacceptable. Each child should be treated individually and here is where the common sense of the nurse is of utmost importance. For a child in an oxygen tent lollipops are invaluable. They not only furnish carbohydrate, but also a thoroughly familiar and enjoyable contact with the outside world.

In the more severe cases when vomiting or dyspnea prevents taking adequate quantities of fluid, the intravenous drip is life-saving. This may be given as normal saline, 10 per cent glucose solution, saline mixed with equal parts of 10 per cent glucose, or Hartmann's solution with glucose in those cases tending toward acidosis. The drip should average about 60 drops a minute. One must remember that while glucose is life-saving, the more glucose, the more viscid the fluid and the slower the administration. The intravenous drip is a godsend; it supplies the life-giving necessities without overwhelming the circulatory system with sudden large increases in water and carbohydrate. In giving fluid by the ankle veins the foot must be exposed for several hours. I have a feeling that a patient with a temperature of 106° F. would not voluntarily have his foot out of the blankets. I think it is of great importance that the extremity be kept warm with hot water bags or an electric pad during the intravenous administration. However, look out for burns. The skin during this period is very susceptible and has a low resistance to heat.

There is, however, a possibility of giving too much fluid. Vomiting which is supposedly toxic may be a defense against overloading the circulatory system. Certainly the response in this case shows that tolerance was not overstepped.



**Convalescence.**—As soon as a child is convalescing he will automatically want more food, and in my experience meat is one of the most desirable additions. I have found that small quantities of round steak ground are particularly acceptable and easy to digest. However, the nurse cannot conveniently feed the child in an oxygen tent. Under such circumstances do not stand on formality; be human. When the weak trembling little hand cannot carry a fork or spoon to his mouth push the plate of meat into the tent and tell him to use his fingers. The smile of gratitude you receive will amply compensate for the breach of etiquette.

As a rule I do not prescribe egg until the child specifically desires it.

The advances in therapy besides the intravenous drip which were responsible for saving this child's life I think are oxygen and blood transfusion.

**Oxygen.**—Oxygen is indicated whenever the body is laboring under an oxygen deficiency. There is nothing specific about oxygen other than that it keeps the blood aerated, and to that extent relieves circulatory embarrassment. Formerly, I used to withhold oxygen until the patient was cyanotic. Now, I believe it is of value if given in sufficient time to prevent any asphyxia. This does not mean that the child with the ordinary pneumonia, who is running an average course, who is comfortable and who shows no respiratory or cardiac embarrassment needs oxygen. But at the first indication of any air-hunger, I prescribe it.

We usually start with 40 or 50 per cent, and then as the disease becomes less severe, gradually decrease to about 20 per cent before removing the tent. There are advantages and disadvantages to the tent method. Many of the tents are old-fashioned and small and the blast of chilled oxygen focuses on one spot of the chest; they require expert supervision and constant manipulation; they make examination of the patient very difficult; they make it almost impossible for the nurse to bathe and sponge the patient, and they are particularly annoying to irrational patients. Patients in a tent complain

particularly of their lonesomeness and isolation. This is felt even by young children, who in a vague way are forlorn at their isolation from the rest of the world. Putting into the tent a familiar plaything may be almost life-saving. To be able to touch affectionately a beloved doll, or woolly animal or well known book may bring peace to the harried sufferer.

A further objection to the tent is that any careful physical examination requires removal from the tent and that many a nurse in her zeal at making up the bed in the morning, ruthlessly takes the patient out without regard for the abrupt changes in oxygen tension and the sudden demands put upon the circulation when the child is plunged from an atmosphere of 50 per cent oxygen to that of ordinary air. I make it a rule that once in an oxygen tent the patient should be left there. I resent the abrupt changes of environment which must be a great shock to a very sick patient. I instruct the nurses to let the making of the bed go, and do the best they can without disturbing the environment of the child.

On the other hand, once in a modern tent the patient is comfortable. The new tents let oxygen come in from the top gradually and have done away with the draught of chilled air focused on one spot. When handled efficiently, the air is pleasantly cool, moist, and is pleasing to the patient. The oxygen content remains constant, and can be controlled at will.

One must not forget that the temperature in the tent may be considerably cooler than in the outside room. The thermometer should be watched, and the child may need extra covering around the chest.

It seems to me that many of the advantages without so many of the disadvantages might be obtained by oxygen through a nasal catheter. I have had little experience with this but plan to try it in the future. The oxygen can be cooled and moistened just as with a tent, and as most pneumonias occur in winter, the air of the room can be made of any temperature pleasing to the patient. This procedure would have the advantages of economy compared to the exorbitant cost of the tent, and at the same time would permit examination of

the patient, therapeutic procedures and nursing technic without changing the amount of oxygen inspired.

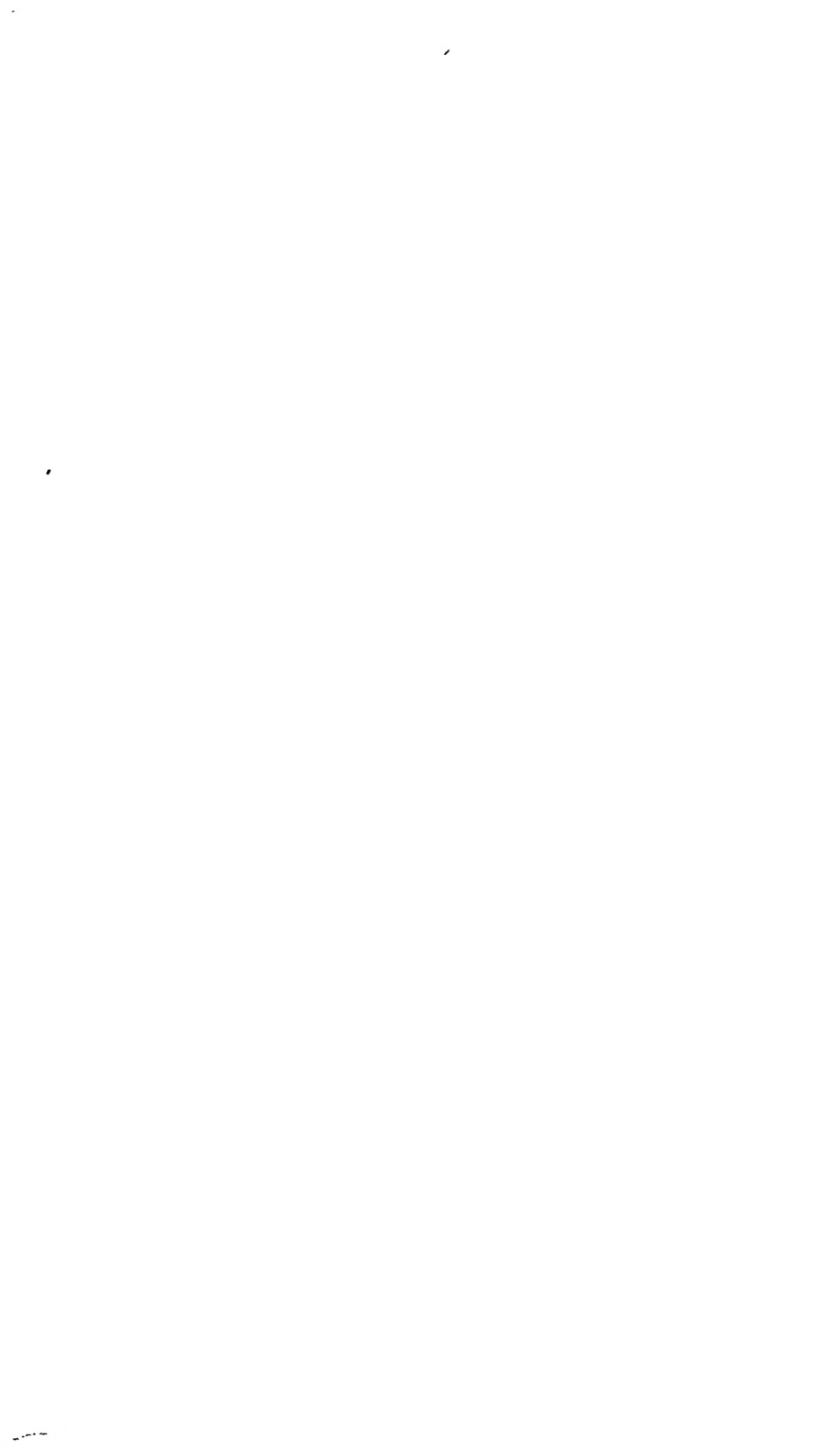
In bronchopneumonia, when the actual accumulation of secretions in the lungs threatens asphyxia, I have found raising the foot of the bed a valuable procedure. Gravity helps drain out the secretions and also gives mechanical support to the coronary circulation.

**Transfusion.**—For failing circulation rather than resorting to drugs, I am using blood transfusion more and more. The subject of shock has interested me ever since my intern days. At that time surgical shock was pointing to the vasomotor center. I learned that medical men were beginning to suspect a similar mechanism in medical shock. My first experiments were with the effects of posture upon blood pressure. During these twenty years medical therapy has consistently adopted every contemporaneous device which might be used to maintain systemic and coronary blood pressure. At present shock is supposedly due to an escape of fluid from the blood vessels into the tissues. Colloidal solutions will remain in the blood vessels longer than ordinary fluids. Salt solutions are of value in combating anhydremia but quickly ooze through the blood vessels and are of no permanent value. Blood, on the other hand, due to its colloidal property will presumably remain longer in the vessels. I sometimes suspect that the value of those antitoxins which are used in large quantities may be to some extent due to this colloidal quality. In this boy 120 and again 150 cc. of blood were given. In addition to the support of the circulation, the blood maintains nutrition and offers an additional reinforcement of leukocytes and red blood cells to replace those destroyed. I believe following a transfusion the appetite unquestionably increases. Then again it is very possible that in a hit or miss way, one may use a donor whose blood contains antibodies. At any rate, I am convinced that transfusions, if given properly and in not too great amounts, are of life-saving value in the severer pneumonias. There is the theoretical danger of cardiac dilatation and overload. I have never seen this occur when the proper precautions as regards technic and quantity were observed.

**Convalescent Serum.**—I cannot close this clinic without a word about convalescent serum. For some years I have been using it in the wards, trying to make up my mind whether it has any value other than that of blood transfusion, and I must confess it is most difficult to form a conclusion. The difficulty at arriving at scientific truth is due to the fact that the present-day pneumonias may be due to so many different types of organisms. I believe there are now some 32 types of pneumococci and I do not know how many types of streptococci and influenza bacilli. To get sputum from a child is by no means easy, and if one does obtain it one cannot be scientifically sure that the organisms found are those which caused the disease. To attempt to stick a swab into the larynx of a desperately sick child is not an ideal therapeutic procedure. We tried to get sputum from this little boy but the effort was so exhausting to him that we did not repeat the attempt, and the report from the swab was "no pneumococci found," although the case was a typical out and out clinical lobar pneumonia. Not only should one know the organisms in the patient but one should know the type of disease formerly present in the donor. Hence, really to get at the matter scientifically requires a very elaborate procedure. However, I have used convalescent serum trying to be as scientific as possible, and still must confess that it seems to be a more or less hit or miss procedure. There are some cases in which the serum may have been of real value. I have seen the temperature drop quite suddenly following injections. But we have all seen that happen without serum. In one patient with a temperature over 107° F. and almost moribund, following a second dose of 100 cc. of convalescent serum intravenously, there was the severest chill I have ever seen, during which the patient almost died. The temperature then dropped to subnormal, then rose in six hours to 104° F., then dropped to normal and remained there. Was this recovery due to the serum? Was this collapse due to poor technic? Ordinarily one should allow an hour for the procedure. Was it an allergic reaction and just an added aggravation during a spontaneous crisis? Your guess is as good as mine. This is

the only case where I have seen any severe reaction following the use of convalescent serum.

In brief, then, I am willing to confess that I am at a loss as yet whether or not to recommend convalescent serum. It may be of value in specific cases. It may supplement blood transfusion. If one by good fortune gets a serum which contains the proper antibodies it may be life-saving. As a general routine, however, without expert supervision for the treatment of the average case seen in ordinary practice and with our present knowledge, I believe that equally good or even better results are obtained by blood transfusion.



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#### NONOPERATIVE (GONADOTROPIC) TREATMENT OF CRYPTORCHISM

SINCE 1930 when Schapiro<sup>1</sup> first reported successful treatment of human cryptorchism by injections of the gonadotropic principle of pregnancy urine, this type of treatment has been applied by a number of clinicians with variable results. As is frequently the case with new therapeutic procedures, the first enthusiastic reports were soon followed by expressions of skepticism and caution. In the meantime sufficient experimental and clinical material was accumulated to allow for a clearer appreciation of the possibilities and limitations of this treatment. To this end it is necessary to keep in mind some pertinent physiological and pathological data.

Normally the testicles descend from the abdominal cavity through the inguinal canal into the scrotum during the seventh to eighth month of intra-uterine life; at birth both testicles are found in the scrotum. Nothing definite was known about the physiological mechanism of the descent of the testicles until 1932 when Engle<sup>2</sup> suggested that maternal gonadotropic hormones play an important part in it. This contention is supported by the following observations: (1) The human is the only organism known in which testicular descent occurs before birth, and the human female is also the only one having gonadotropic hormones in blood circulation throughout the period of gestation. (2) A noticeable increase in the number of the interstitial cells of the testicle of the human fetus occurs one to two months before term; a similar change may be experimentally produced in immature monkeys by injections of the gonadotropic hormone of pregnancy urine. (3) In imma-

ture monkeys and rats injections of the pregnancy urine gonadotropic hormone cause premature descent of the testicles. (4) An analogous phenomenon indicating effects of maternal female sex hormone is occasionally observed in newborn girls showing swelling of the major labia or breasts. These and similar other observations may be considered as sufficient evidence to indicate that in the normal fetal descent of the testicles gonadotropic hormones of the mother are instrumental.

If the testicle fails to descend before birth, it usually remains undescended until the beginning of puberty. The descent may be arrested at any point, in some cases in the abdominal cavity, more often in the inguinal canal. The arrest may be bilateral, both testicles being arrested at the same point or at different points. In the majority of the cases unilateral arrest is observed, the other testicle being in normal position. Drake<sup>3</sup> observed 11 cases of cryptorchism among 260 boys nine to nineteen years of age—a frequency of 42 per thousand. It has been known for many years that spontaneous descent of undescended testicles may occur at puberty, but the frequency of this phenomenon was not realized until recently. It appears that spontaneous pubertal descent occurs in the majority of cases of cryptorchism; it occurred in 9 out of 11 of Drake's cases. This is confirmed by the fact that cryptorchism is not nearly as frequent in the adult population: extensive statistics obtained on army recruits in different countries indicate an incidence of 2 to 5 per thousand.

While the normal fetal descent of the testicle occurs under the influence of maternal gonadotropic hormones, late spontaneous descent in puberty is thought to be brought on by the gonadotropic hormone of the hypophysis of the individual.

Histologically the undescended testicle, prepubertal or postpubertal, shows a picture similar to that of a normal prepubertal scrotal testicle. In other words, the undescended testicle fails to supply at puberty its seminiferous tubules with normal germinal epithelium, and remains aspermic and sterile. It has been shown conclusively by Moore<sup>4</sup> that scrotal position is necessary for the normal development of the germinal



epithelium because of the lower temperature it insures. If a mature scrotal testicle with the spermatic cord intact is placed in the abdominal cavity, soon most of the germinal epithelium degenerates and disappears; replacement of such a testicle into the scrotum is followed by regeneration of the germinal epithelium and spermatogenesis. However, the abdominal testicle may produce male sex hormone in apparently undiminished amounts, as demonstrated by Moore in experiments on guinea-pigs.

**Classification.**—*Group A.*—In a number of cases of human cryptorchism examination of the patient fails to disclose any additional pathology of importance. There are no signs of disturbance of the endocrine system; growth, sexual and mental development are normal. Puberty appears in due time with all secondary sex characteristics and sexual potency. The majority of unilateral cryptorchism cases and a few of the bilateral ones belong to this category. Failure to descend may be due to causes of local anatomical nature, such as developmental error, or adhesions due to fetal peritonitis; in these cases spontaneous late descent at puberty will not occur. In other cases descent is arrested before birth because of deficiency in maternal gonadotropic hormones; late spontaneous descent frequently sets in at puberty under the stimulation of the normally functioning anterior pituitary. Clinical differentiation between these two subgroups can, as a rule, not be made before puberty.

*Group B.*—In most cases of bilateral cryptorchism clinical examination reveals more or less marked signs of hypogonadism. The scrotum is undeveloped, the penis is infantile, the prostate and seminal vesicles are hypoplastic. The patient is more or less obese with a girdle type of fat distribution. Puberty is delayed and imperfect, or entirely missed. Late spontaneous descent rarely occurs. The undescended testicle remains not only sterile but also deficient in the production of the male sex hormone on which the development of the secondary sex characters depends.

The hypogonadism is usually secondary, being due to

deficient gonadotropic activity of the hypophysis; it is frequently accompanied by signs of deficiency of other functions of the hypophysis, such as stunted growth, diabetes insipidus, subnormal mentality, delayed dentition, etc. The question arises whether the fetal arrest of testicular descent is also due to the pituitary deficiency. There is no evidence that the hypophysis of the fetus has any active rôle in the physiological mechanism of testicular descent. Furthermore, a number of cases of most severe hypopituitarism are born with scrotal testicles, even though the further development of these testicles will be seriously impaired. Accordingly, it must be assumed that the fetal arrest of descent is independent from the pituitary failure of the patient in cases of hypogonad cryptorchism. On the other hand, the absence of late spontaneous descent is obviously a consequence of the patient's deficient pituitary gonadotropic hormone production.

In some cases cryptorchism is associated with primary hypogonadism: there is congenital idiopathic hypoplasia of the testicles, or atrophy following orchitis as a complication of mumps, etc. The gonadotropic activity of the anterior pituitary is intact in these cases. Clinically they usually present the picture of eunuchoidism with the typical body proportions and delayed union of epiphysial junctions. Differentiation between primary and secondary hypogonadism, associated with cryptorchism, may be difficult in some cases.

**Specificity of Gonadotropic Therapy.**—Injections of gonadotropic hormone preparations in cryptorchism have been followed in many cases by descent of one or both testicles. Some doubt has been expressed as to the specificity of this effect in view of the fact that spontaneous descent frequently occurs; the result might be merely coincidental. However, a number of observations are available which would be difficult to explain on the basis of coincidence: (1) In many cases gonadotropic therapy was followed by descent of the testicles in four- to six-year-old boys, and in some cases in eighteen- to twenty-seven-year-old men, *i. e.*, at ages when spontaneous descent very rarely occurs. (2) Results were frequently ob-

served within two weeks of treatment. (3) In some cases descent occurred during treatment but the testicle again retracted into the inguinal canal or abdominal cavity shortly after the injections were discontinued. A second course of injections brought the testicle down again. (4) Cases were observed that were previously operated on, the testicle being placed in the scrotum; subsequent retraction occurred; gonadotropic treatment was followed by descent. In view of such observations it is safe to say that descent of cryptorchid testicles may be the direct result of gonadotropic therapy.

**Indications for Gonadotropic Therapy.**—Obviously, gonadotropic treatment is indicated in all cases belonging to Group B, although favorable results are not always obtained. Why treatment fails in some patients of this group is difficult to say. Possibly, in some cases, local anatomical causes exist in addition to the deficiency of the anterior pituitary. In primary hypogonadism (eunuchoidism) the lesion of the cryptorchid testicle may be so severe as to obviate response to the strongest gonadotropic stimulation. In other cases the intensity or duration of the treatment might have been insufficient.

In some patients belonging to Group A gonadotropic treatment is doomed to failure because of the presence of anatomical obstacle. In other cases of this group treatment is superfluous as descent will spontaneously occur at puberty. Only in a relatively small number of cases is hormonal treatment both necessary and successful. Unfortunately, the nature of the case is not, as a rule, recognizable before puberty. Accordingly, correct indication for hormone therapy can hardly be made when the patient is seen before puberty. If cryptorchism persists in the presence of more or less marked pubertal changes, a trial with hormone therapy is indicated. Failure of this therapy may be considered as evidence of anatomical obstruction and indication for surgical interference.

Postoperative hormonal treatment—following orchiopexy—has been advocated to insure against possible retraction of the testicle (Spence and Scowen<sup>7</sup>).

At what age should treatment be started? Cryptorchism is an abnormal condition at any age and it might seem logical to attempt to correct it as early as possible. In fact, several clinicians expressed this opinion and a number of four- to ten-year-old successfully treated children are on record. It is not quite clear to me what is to be gained by producing testicular descent artificially at this early age unless some special indication, such as local pain, or hernia exists.

For cases of Group B with marked genital dystrophy (undeveloped scrotum and penis) advisability of early treatment may be a matter of opinion: the testicle in these patients is not only undescended but hypoplastic as well; chances for spontaneous late correction are slight. Yet, even in these cases treatment at the normal beginning of puberty—eleven to thirteen years—rather than earlier appears to be the logical procedure.

For Group A early treatment is hardly justified. As I mentioned before, a normal prepubertal undescended testicle does not differ histologically and functionally from a normal prepubertal scrotal testicle, and scrotal position becomes of great importance for the structure and function of the testicle only with the onset of puberty. In patients of Group A, general development, including sexual development proceeds normally whether the testicle is in the scrotum or in the abdomen. Furthermore, in many instances spontaneous descent occurs at puberty. Accordingly, there is no reason why one should not wait with treatment of patients of this group until puberty is well established, at fourteen or fifteen. It is probably not advisable to wait much longer. I have found no report in the literature of successful treatment of patients older than eighteen, belonging to this group.

**Some Technical Details of Hormone Therapy.**—Most authors used preparations of the pregnancy urine gonadotropic hormone (prolan, anterior pituitary-like substance). Others used extracts made from the anterior lobe of the hypophysis. There is no evidence that either one is superior. In the presence of signs of hypothyroidism desiccated thyroid gland may be given simultaneously.

Injections of the pregnancy urine gonadotropic hormone are given daily or every other day subcutaneously or intramuscularly, 100 to 300 rat units each time. The duration of treatment and the total amount of the hormone administered varies greatly. In some cases a few hundred units given within two weeks prove sufficient. In other cases (Group B) treatment was continued for over a year with a total amount of 20,000 or more units injected. It is probably safe to say that if the injection of 10,000 units fails to produce any change, further treatment at that time is not likely to succeed. In such cases it may be advisable to undertake a second course of injections starting a few months later, as suggested by Spence and Scowen.<sup>5</sup> They quote the work of Sellye *et al.*,<sup>6</sup> who have shown that after prolonged administration of gonadotropic hormone virgin female rats become temporarily insensitive to the hormone. Repetition of treatment is also indicated when the testicle which has descended after a course of injections, later retracts into its previous position. As a rule, treatment is discontinued as soon as the testicle reaches the bottom of the scrotum, although in cases associated with sexual infantilism it may be necessary to continue hormonal treatment over a longer period.

**By-effects of Hormone Therapy.**—In some cases mild to moderate pain is complained of in the groin of the affected side during treatment. This does not necessitate interruption of treatment as the pain soon subsides.

After the testicle has descended it is usually smaller than normal but soon reaches normal proportions. Enlargement beyond the normal for the patient's age is not produced even when treatment is continued with large doses. The same is true for the scrotum and penis. Precocious secondary sex characteristics—such as pubic hair, mutation of voice, etc.—in children treated before puberty were not observed, except by Dorff<sup>7</sup> who gave very large amounts of the hormone (as much as 46,000 units). Neither is enlargement of the prostate or of the breasts of the patients reported, although Geschickter *et al.*<sup>8</sup> reported such effects in monkeys treated with large amounts of pregnancy urine hormone.

The question whether the testicle, which has descended into the scrotum in response to hormonal therapy, becomes fertile cannot be answered directly at this time. Some indirect evidence is available. Thus it is known that bilateral undescended testicles brought down into the scrotum by surgical orchiopexy may become fertile (MacCollum<sup>9</sup>). Brosius and Schaffer<sup>10</sup> reported a case of bilateral testicular atrophy with complete aspermia following orchitis as a complication of mumps, in which gonadotropic hormone therapy repeatedly produced extensive spermatogenesis.

Huberman<sup>11</sup> and Dorff<sup>7</sup> noticed marked improvement of mental development and enuresis nocturna in some of their cases treated for cryptorchism. Accelerated growth is sometimes observed. It appears that when the gonads mature under gonadotropic treatment, they exert a stimulating influence on growth, probably by way of the anterior lobe growth-promoting apparatus.<sup>12</sup>

Gonadotropic treatment has no effect on the obesity associated with genital dystrophy. The obesity and the type of fat distribution usually persist even after complete correction of cryptorchism and sexual underdevelopment. Neither is there any definite change in basal metabolism.

A unique observation of enuresis, polydipsia and glycosuria appearing during gonadotropic treatment for cryptorchism in a thirty-month-old child is reported by Koplin<sup>13</sup>; all symptoms disappeared after three weeks following the termination of treatment. This may be considered as another reason against gonadotropic therapy at early age.

#### PRESENTATION OF CASES

**Case I.**—This boy is now thirteen years old. He is normally developed. Both testicles are in the scrotum; their size is normal for his age. He was a normal boy when I saw him first about a year ago, except for a unilateral cryptorchism. The left half of the scrotum was empty, as was the left inguinal canal. We gave him injections of 200 units antuitrin-S three times a week. After the sixth injection the left testicle de-

scended into the scrotum and soon reached the size of the right testicle. I have no doubt that the gonadotropic therapy was instrumental in the descent of this testicle, although it is quite possible that descent would have occurred by this time, or later, without any therapy. We now believe that such cases do not need treatment before they reach their fourteenth or fifteenth year.

**Case II.**—This boy is twelve and one-half years old. He has bilateral cryptorchism; no trace of the testicles can be found on physical examination. Otherwise he is normally developed in every way. We have started with gonadotropic therapy five months ago, giving him daily injections of 100 units antuitrin-S. On the tenth day I found the right testicle in the scrotum, the left testicle in the inguinal canal. After waiting for four weeks without noticing further change, we gave him again daily injections of the same substance and amount. Two weeks later both testicles were in the scrotum. He has received altogether 2400 units of the hormone. Now he returns with both testicles retracted into the abdominal cavity. Another course of injections would probably bring these testicles down again, and with continued treatment they might stay in the scrotum permanently. But we might as well wait for a year or two without treating this patient. In the meantime the testicles may spontaneously descend. If this will not occur, we will then try another course of hormone injections. Small amounts of the hormone will probably suffice at that time to insure permanent result.

**Case III.**—Two years ago this patient presented a typical picture of adiposogenital dystrophy. He was then thirteen years old, his height was 63 inches, his weight 123 pounds. The scrotum and penis were markedly underdeveloped; a tiny structure, of the size of a small pea, was found in the left half of the scrotum; the right half of the scrotum and the right inguinal canal were empty. He had an average intelligence. His basal metabolism was  $-26$  per cent. His bone development was two years advanced as indicated by x-ray pictures of his hands and

lower arms, a finding which is not infrequently associated with genital underdevelopment.

Gonadotropic treatment was started in March, 1934. He received daily injections of antuitrin-S, 100 units each time for thirty days. At the end of this period I found both testicles in the scrotum; they were not larger than small peas. After four weeks we gave another course of 20 injections in the same way as before. After another month we tried an anterior pituitary gonad-stimulating preparation, prephysin, which was given in daily injections, 25 units each, for six weeks. Altogether he received 11,200 units of antuitrin-S and 1050 units of prephysin. There was no further change, and we decided to wait for a while. About a half year later, in May, 1935, the right testicle was much larger, of the size of a cherry, the left remained as small as it was. The penis and scrotum have shown some development, and there was some pubic hair. It appeared that he was entering puberty and we again decided against interference. As you can see from his present state, this was justified. The appearance of his external genital organs is now almost normal: both testicles in scrotum, the right testicle is of normal size and consistency, the left is somewhat smaller and softer. The penis is of normal size, and there is pubic hair present. His voice is in mutation. His height is now 68 inches, weight 131 pounds, basal metabolic rate —20 per cent.

We believe that the prompt descent of the right testicle, after one month's treatment, was due to the gonadotropic therapy. Whether this therapy was also instrumental in bringing about his puberty is open to question. We have in our care another boy, now eighteen years old who five years ago was a typical case of adiposogenital dystrophy and who at fifteen entered puberty and eventually showed perfect genital development, without any treatment whatsoever. Undoubtedly, in some cases of adiposogenital dystrophy spontaneous adjustment occurs at puberty.

As you see, the patient is still obese, and I may add that his type of fat distribution, thought to be characteristic for adiposo-



genital dystrophy, is quite the same as it was two years ago when he was sexually infantile. This indicates that the hypogonadism is not the cause of the obesity with which it is so frequently associated.

**Case IV.**—This boy was first seen fourteen months ago when he was fourteen years old. He had bilateral cryptorchism. The small and empty scrotum was in peculiar contrast to the large penis. There was no pubic hair. A slight but definite gynecomastia was present. He was undersized, his height being 57 inches. He was obese, weighing 118 pounds. There was marked delay in dentition. His intelligence was definitely subnormal. Basal metabolic rate was —6 per cent. I classified the case as a cretinoid.

Starting in February, 1935, he received 5600 units of antuitrin-S and 250 units of prephysin within three months. At the end of this period a cherry-size testicle was found in the right side of the scrotum; the left testicle was still missing. Pubic hair appeared. In September, 1935, we gave another course of injections, 1400 units of antuitrin-S in three weeks. There was no immediate change, but a half year later, now, the right testicle is of normal size, in the scrotum, and the left testicle about half as large, in the inguinal canal. His height is 61 inches, a growth of 4 inches in fourteen months, which is rather remarkable in view of his slow growth before. His weight is 122 pounds. The gynecomastia is hardly noticeable now. There is no apparent change in his mental capacity.

**Case V.**—This young man is twenty-one years old. He was admitted to the clinic two years ago. He complained of severe nosebleeds and extensive subcutaneous hemorrhages which were found to be due to thrombocytopenic purpura. In addition, he had a unilateral cryptorchism. The right testicle, penis, prostate, pubic hair, and sexual manifestations were normal; the left testicle, of the size of a cherry, was found in the middle of the inguinal canal.

Four thousand units of antuitrin-S were administered within two months, without noticeable effect. Half a year later 11,000

units of antuitrin-S were injected within four months. As you see, the cryptorchism persists. We may conclude that in this case an anatomical obstruction exists which cannot be eliminated except by surgical intervention.

**Case VI.**—You will recognize this case by inspection as that of eunuchoidism. He is thirty-three years old. He is tall and obese with a female type of fat distribution. His extremities are relatively long, the trunk relatively short. There is very little pubic hair and no body hair; he shaves once in two weeks. The penis and scrotum are infantile, the prostate is hardly palpable. There is a scar in the right inguinal region; he was operated on that side for cryptorchism at thirteen, unsuccessfully; there is no trace of the right testicle. In the left inguinal canal a small firm structure, of the size of a navy bean is palpable. He complains bitterly of his greatly impaired sexual ability.

We have given this patient in the past two years 27,000 units of antuitrin-S and 1000 units of prephysin. He noticed occasional slight pain in the left groin, faster growth of facial hair, and more frequent sexual manifestations. But the testicle is as small as it was before, and remains in the inguinal canal. We advise orchiopexy to be followed immediately by gonadotropic therapy. This may help if viable testicular tissue is still present in the structure palpable in the inguinal canal.

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## CLINIC OF DR. AARON ARKIN

COOK COUNTY AND MT. SINAI HOSPITALS

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### ESSENTIAL HYPERTENSION AND CARDIOVASCULAR- RENAL DISEASE

THIS clinic will be devoted to a discussion of essential hypertension and cardiovascular-renal disease.

Essential hypertension or primary arterial hypertonia is a cerebral functional disorder affecting the vasomotor apparatus, and is characterized by a hypertonus of the arterial system. This hypertonus leads to a progressive increase in the systolic and diastolic blood pressure, followed by cardiac hypertrophy and cerebral, renal, retinal and other vascular changes. The disease often continues for years without producing any subjective symptoms and is frequently diagnosed at a late stage when cerebral, cardiac, renal, or ocular symptoms appear. The diagnosis in the early or functional stage can be made by finding an increased tonicity of the arteries with a variable hypertension, spastic retinal arteries with tortuosity of the venules, and beginning hypertrophy of the left ventricle. The diagnosis in the advanced or organic stage is based upon the presence of a more or less fixed high systolic and diastolic blood pressure, rigid arteries, marked cardiac enlargement, hypertensive retinitis, and eventually signs and symptoms of cerebral, cardiac, or renal disease.

In making a diagnosis of essential hypertension it is naturally assumed that other causes of hypertension such as: (1) glomerular nephritis, (2) polycystic kidneys, (3) urinary obstruction, (4) increased intracranial tension, (5) eclampsia, (6) adrenal tumors, (7) pituitary basophilic adenoma, (8) lead poisoning, (9) periarteritis nodosa of the kidneys, (10)

polycythemia, and (11) coarctation of the aorta, are excluded whenever possible.

In exceptional cases the disease may run a more acute rapidly fatal course. This is due to extensive renal arteriolar changes which lead to extremely high blood pressure readings and death from renal decompensation, acute cardiac failure, or cerebral hemorrhage. On the other hand, the hypertension in the chronic cases frequently decreases with myocardial damage and many patients in the late stage present little or no hypertension. But these persons have a large heart, retinal changes, a relatively low pulse pressure, and evidence of cardiac failure usually without valvular heart disease. A rheumatic or luetic heart disease may be aggravated by an arterial hypertonia.

A better understanding of the nature of essential hypertension will benefit the many sufferers from this ailment. Fewer costly and often harmful drugs will be used in this disease, for which there is no specific cure. We shall see that a suitable restful régime of reduced mental and physical strain, rest periods and increased hours of sleep, and reassurance by the physician constitute the treatment of primary arterial hypertension. The drugs of chief value are sedatives, and those which lower the blood pressure in vascular crises. Marked lowering of pressure in advanced hypertension is usually harmful rather than beneficial.

#### THE NORMAL BLOOD PRESSURE

The normal blood pressure in adults, of 120 to 150 systolic and 80 to 95 diastolic, is maintained by the tonus of the arterioles and the action of the heart. It is subject to considerable psychic influence. The arteriolar tonus is regulated by the action of the vasodilator and vasoconstrictor impulses from the central nervous system. The diastolic pressure is a measure of the peripheral resistance within the vascular system, the systolic pressure measures the total contractile force of the left ventricle. Unfortunately we have no means of measuring the systolic and diastolic pressure in the pulmonary artery of the right heart. The blood pressure in the pulmonary

artery is normally about one third that of the aorta, hence the right ventricle is normally thinner than the left and the right coronary artery usually presents less atherosclerosis than the left.

The pulse pressure, or difference between the systolic and diastolic pressure, measures that portion of the ventricular force which is available for propelling the blood through the vascular tree. It is normally about one half of the diastolic and one third of the systolic pressure. This is the well-known 1-2-3 relationship which is found in normal persons.

### THE NATURE OF ESSENTIAL HYPERTENSION

The etiology of primary arterial hypertension has not yet been entirely solved by experimental, clinical, or anatomical studies. Four endocrine glands have frequently been blamed, the adrenal, pituitary, thyroid and sex glands. Many workers have been concerned with the study of the blood for substances acting on the blood vessels. A specific pressor substance has not been found in the blood of hypertensives. Hypertonus of the walls of the circulatory apparatus occurs in two forms. There is an arterial form, and a generalized form which involves the entire circulatory system. We wish to discuss the first type, primary arterial hypertonia or essential hypertension. The second type is the toxicogenic or renal type.

Hypertension is a symptom of the hypertonus of the arteries of the systemic circulation. Without an increased tonicity or hypertonus of the arterial and arteriolar walls there can be no high blood pressure in essential hypertension. But hypertonus can occur without high blood pressure when only a part of the peripheral arterial system is affected, or the heart has become decompensated. The hypertonus, especially in the early stage, varies in its intensity and distribution. When a large vascular area such as the splanchnic is involved the blood pressure will rise; when a small area such as an extremity or a single organ is affected there may be little or no rise of blood pressure. When the hypertonus becomes persistent and leads to a hypertension the heart, blood vessels, brain, kidneys, eyes

and other organs suffer organic changes. There is an increased susceptibility of the arterial walls to spasms, producing harmful angiospastic crises with further circulatory derangement and dangerous rises in blood pressure. Such crises, according to Pal, may be regional or generalized.

Essential hypertension often commences in young adults with an hereditary predisposition. The most important factor is the psychic influence. Most of the patients are neurotic and temperamental. The most frequent subjective symptoms are headaches, vertigo, and irritability. The individuals are easily upset, often suffer from migraine headaches. Pain in the back of the neck or occipital region is common. Some complain of palpitation of the heart, especially when lying on the left side. Blood pressure readings will show marked variations in the systolic and diastolic pressure. Excitement or aggravation frequently causes rises of 20 mm. or more, rest or sleep a return to normal. A systolic pressure above 150 mm. with a diastolic above 95 we consider to be an hypertension. In severe cases of malignant nephrosclerosis we often see systolic pressures above 250 and diastolic above 160 mm.

In essential hypertension there is an increased peripheral resistance which must be overcome to maintain an adequate circulation. The resistance manifests itself by a rise in the diastolic pressure. This leads to hypertrophy of the left ventricle. As long as the heart can increase its force and maintain an adequate pulse pressure the individual may suffer few or no symptoms. When the heart begins to fail there is a reduction in the systolic pressure, which means the pulse pressure is lowered. Since the diastolic pressure can fall very little or not at all, the decrease in the systolic pressure is at the expense of the pulse pressure and must end in circulatory failure. As long as the hypertrophied heart can maintain a pulse pressure approximately one half as great as the elevated diastolic pressure a fairly adequate circulation is maintained. This explains why some hypertensives can carry on for ten or twenty years or longer with diastolic pressures of 110 to 130 and systolic pressures of 180 to 200.

## THE HEART IN ESSENTIAL HYPERTENSION

In essential hypertension there is a progressive increase in the tonus of the arteries and arterioles which produces a swelling of the walls with constriction of the lumen. At first this process is reversible, but later the walls become thickened with permanent narrowing. The increase in the systolic and diastolic blood pressure leads to a remarkable adaptation of the heart and circulation. In spite of high pulse pressures the heart rate, stroke volume, minute volume output of the heart, and the blood volume remain essentially normal.

The heart muscle undergoes a compensatory hypertrophy, perhaps also an increase in tonus of the musculature. The hypertrophy is at first concentric with marked thickening and some shortening of the muscle fibers, later eccentric with elongation of the fibers. The cardiac hypertrophy, which is so essential in overcoming the increased peripheral resistance, unfortunately also leads to eventual cardiac decompensation unless the patient succumbs to a cerebral insult or renal failure. The heart often does its greatly increased work for ten, twenty or more years before the symptoms of failure appear. During all this time the person may not be aware of any primary arterial hypertension unless the blood pressure is taken or the eyes are examined.

I have for over a decade called attention in my clinics to the fact that essential hypertension is one of the chief causes of cardiac failure, and that 65 per cent of hypertensives die from heart disease. Today one fourth of all deaths in people above the age of fifty years are due to hypertensive heart disease. I have also emphasized the fact that the marked myocardial hypertrophy leads to insufficiency of the coronary blood supply. The muscle cells often increase to two or three times their former size and suffer from a relative anoxemia which leads to their degeneration and fibrosis. The anoxemia explains the cardiac failure in many hypertensives who reveal little or no coronary sclerosis at necropsy. When we add to the anoxemia of marked hypertrophy the further factor of coronary arteriolar spasm with marked reduction of the blood flow, it is not difficult

to explain myocardial failure with little or no gross coronary disease. The many hypertensives who survive for years and are past the fifth decade of life will of course present different grades of coronary sclerosis. Coronary thrombosis or embolism may cause myocardial infarction. The heart may reach a tremendous size, and often weighs 600 to 800 Gm.

**Case I.**—Mr. E. A. G., fifty-five years of age, states that he was well until six months ago. At that time he developed pain in the heart region with radiation to the left arm and neck. The pain was induced by physical exertion, and disappeared with rest. Now the pain is more severe, lasting ten to twenty minutes and occurs several times a day. There is a marked nocturnal dyspnea and insomnia. The patient cannot lie on his left side on account of palpitation of the heart.

The patient was told five years ago that he had a high blood pressure and was refused life insurance. Since that time he had been able to attend to his duties as a dairy inspector.

There is a moderate cyanosis and dyspnea. The pupils react normally to light, the patellar reflexes are normal. The fundi reveal a hypertensive retinitis, with narrow arteries, exudates and small hemorrhages. The pulse rate is 96, with occasional extrasystoles. The radial arteries are very firm, and difficultly compressible. The blood pressure is 188 systolic and 128 diastolic. The heart is of the aortic type with a transverse diameter of 7 inches (orthodiagram). The aortic second sound is loud and ringing, there are no murmurs. The liver is palpable 1 inch below the costal margin. There is slight edema of the legs. There are moist râles at both lung bases. Wassermann and Kahn tests are negative. The urine contains a trace of albumin and a few casts. The blood non-protein nitrogen is 45 mg.

The patient improved for a time with bed rest, aminophyllin, and digitalis. The anginal pains disappeared with more marked evidence of cardiac failure. The blood pressure dropped to 148 systolic and 110 diastolic.

The diagnosis was essential hypertension, with marked



cardiac hypertrophy and dilatation, angina pectoris, and cardiac decompensation. The patient died suddenly of cardiac failure. The necropsy revealed primary contracted kidneys of hypertension, marked hypertrophy and dilatation of the heart which weighed 750 Gm., and practically no sclerosis of the coronary arteries. The heart muscle presented a marked diffuse fibrosis. There was no valvular disease.

This case illustrates one of the most frequent causes of cardiac failure, with attacks of angina pectoris. The cause of death was the severe anoxemia of the greatly hypertrophied heart with practically no coronary disease. The patient knew of his hypertension for five years, but probably had it a much longer time.

#### THE BRAIN IN ESSENTIAL HYPERTENSION

One fourth of all persons with essential hypertension die from cerebral changes which are chiefly hemorrhage or encephalomalacia. Here as in the myocardium degeneration is often found in the presence of normal arteries, again indicating that blood vessel spasms produce the lesions. Such spasms or vascular crises will lead to necrosis and softening if the blood supply is cut off for more than a minute or two. That cerebral vascular spasms are frequent in essential hypertension is indicated by the many transient cerebral symptoms. I have often seen paresthesias, motor aphasia, monoplegia, hemiplegia, twitchings in single muscle groups, epileptiform seizures, severe migraine headache, vertigo and sudden blindness appear and disappear in these patients. We shall see that some of these symptoms may lead to the mistaken diagnosis of brain tumor or hemorrhage. In some of these patients there is an increased pressure of the cerebrospinal fluid, with some relief from spinal puncture. These cerebral manifestations, sometimes called hypertensive encephalopathy, may be premonitory symptoms of more serious brain involvement.

Cerebral hemorrhage and thrombosis are the most frequent cause of death in the cerebral type of essential hypertension. The favorite site of hemorrhage is the region of the basal

ganglia. Here the blood vessels have large perivascular spaces, and the surrounding brain tissue has a poor blood supply. Small areas of softening combined with a sudden increase of blood pressure will cause rupture with hemorrhage. Often the vessels are sclerosed. The most common cause of cerebral hemorrhage is hypertension. A sudden severe headache or vomiting at the onset is strongly in favor of the diagnosis of hemorrhage. Unconsciousness or coma develops in 70 per cent of the hospital cases. A bloody spinal fluid, stiffness of the neck, a high leukocyte count, systolic blood pressures of 200 or above, loss of pupil reflexes, dilatation of one pupil, and positive Babinski sign are the usual findings in cases of cerebral hemorrhage.

**Case II.**—This case is very instructive because a diagnosis of brain tumor was made by two neurologists who advised operation.

The patient, a white male, fifty-three years old, was first seen in August, 1928. At that time he stated that he was refused life insurance by two companies on account of his blood pressure and heart condition. Since 1920, he had occasional dizzy spells lasting one-half to one hour. He is a very nervous, easily excitable person, eats rapidly and irregularly and is unable to relax. The blood pressure in August, 1928, was 160 systolic and 105 diastolic. The heart was slightly enlarged with rounding of the left ventricle. There were no murmurs. The aortic second sound was accentuated. All reflexes were normal. The fundi revealed spasm of the arteries with tortuous veins around the macula. The Wassermann was negative, urine normal.

The patient was advised of the importance of keeping serene, rest periods, and mental relaxation. He felt well for two years, the blood pressure varying between 150 and 190 systolic pressure, and 95 and 110 diastolic. In April, 1931, the patient had severe occipital headaches, pain in the back of the neck, left shoulder and left arm. There were two attacks of cardiac pain lasting five to ten minutes. The blood pres-

sure had risen to 200 systolic and 130 diastolic. With sedatives, metaphyllin and occasional use of erythrol tetranitrate the patient felt quite well for four years. The blood pressure was around 170 systolic and 120 diastolic. The patient received streptococcus vaccine from another physician for his arthritic and neuralgic pains with some benefit.

In January, 1936, the patient went to the bathroom and developed a sudden blindness. He got into bed and stayed there several days. After three days' rest the blood pressure was 200 systolic and 130 diastolic. He developed severe frontal and occipital headaches. Examination revealed no evidence of sinus infection. On February 13th, the patient noticed a numbness of the right side of the body and weakness of the right hand. At times he dropped things. On February 17th, he had a severe headache in the left temporal region with loss of speech. While talking on the telephone he suddenly found himself unable to express his thoughts, though fully aware of his surroundings. For a week there were intermittent attacks of the motor aphasia. At times there was a twitching of the right arm and leg, with weakness. Two neurologists were consulted who diagnosed a brain tumor in the left temporal region and advised operation. There was no choked disk! The writer held to his diagnosis of hypertensive encephalopathy with cerebral-vascular spasms and intermittent motor aphasia and paresis. A third consultant agreed. The patient's symptoms disappeared the next day with rest in bed and the administration of theominal. From February to July, 1936, the patient has felt well, and there have been no recurrences of the motor aphasia or paresis. The patient is resting much of the time, and usually feels better in warm weather. The blood pressure is now 170/120.

The above case is an excellent example of the cerebral form of essential hypertension, most likely due to cerebral vascular crises with spasms of the cerebral vessels, perhaps even minute hemorrhages, or areas of softening. Nevertheless the patient's symptoms all disappeared. We may add here that patients with essential hypertension are poor surgical risks especially

for brain surgery, and that one should be very hesitant in making a diagnosis of brain tumor in a hypertensive, with hypertensive retinitis but no choked disk. Even the presence of choked disk may be due to the cerebral edema of hypertension.

**Case III.**—This man, forty-five years old, was referred for examination on January 24, 1935. His mother, seventy-two years old, has had hypertension and heart disease for twenty years. The father has diabetes and obesity. Seven years ago the patient obtained life insurance. Four years ago he was refused because of obesity and hypertension. One year ago he developed a left facial paralysis which disappeared after six weeks. In September, 1934, the patient had several attacks of severe abdominal pain diagnosed as renal colic; they were accompanied by slight hematuria. At the same time there were severe occipital headaches, and twitchings of the left arm and leg for one week. The patient's vision became poorer and his glasses were changed.

The examination on January 24, 1935, revealed a moderate obesity, pendulous abdomen, and pectoral alopecia. The pupils reacted normally to light. Fundus examination revealed a marked neuroretinitis. The blood pressure was 230 systolic and 150 diastolic. The heart was of the aortic type with a transverse diameter of 6 inches. There was a very loud ringing aortic second sound, no murmurs. The liver and spleen were not palpable. There was no edema. The left arm and leg became spastic at times with exaggerated reflexes. The Wassermann was negative. The blood sugar and nonprotein nitrogen were normal.

With rest, phenobarbital, and erythrol tetranitrate the patient improved. The twitchings disappeared, as did the headaches. The patient returned to work against my advice. The twitchings of the arm and leg returned, and the blood pressure rose again from 190/130 to 240/160. The patient developed an upper respiratory infection with fever and the blood pressure dropped to 200/140. On April 25th, the patient complained of considerable dyspnea, and some cardiac pain

on exertion. The blood pressure was 240/160. He was ordered to bed and improved. Two months later the patient, suspecting that his condition might be serious, decided to visit his mother in the East. After a long automobile trip he complained of intense headache and died of a cerebral hemorrhage. The clinical diagnosis of essential hypertension, with marked cardiac enlargement, arteriolosclerotic primary contracted kidney, and cerebral hemorrhage was confirmed at necropsy.

### THE KIDNEY IN ESSENTIAL HYPERTENSION

The third organ affected in primary arterial hypertension is the kidney. As Pal stated about thirty years ago, the kidney changes are not the cause of the hypertension. In the early stage there are no organic kidney changes. As the disease progresses arteriolar hypertrophy and fibrosis, or arteriolosclerosis, develop and reduce the blood supply to these vital organs. We have then the primary contracted, red granular kidney of essential hypertension. This process may be very slow extending over years. In about 10 per cent of cases the renal changes are rapid and lead to decompensation with uremia. This form, seen most often in young adults, especially negroes, is called malignant nephrosclerosis or malignant hypertension. These patients have a generalized more severe hypertonus of the entire vascular system, with angiospastic crises. The highest blood pressures which we find are usually in this form. Systolic pressures of 250 or more and diastolic pressures above 160 are not uncommon. This is the pale hypertension of Volhard, which may be called toxigenic or renal hypertension in contrast to the primary arterial.

The renal or toxigenic hypertension is more generalized and more rapid in its development. It affects the heart muscle, arteries, arterioles, and venous system. The entire cross section of the vascular apparatus has become smaller. The heart reveals the characteristic concentric hypertrophy, with very thick wall and relative reduction in the size of the ventricular cavities. The patient does not live long enough to get an eccentric hypertrophy. Sometimes a glomerulonephritis is grafted upon the so-called "malignant" nephrosclerosis.

The chronic or so-called "benign" nephrosclerosis, which is found in most cases of primary arterial hypertension at necropsy, may become aggravated by failure of the heart or too marked lowering of the blood pressure by vasodilator drugs. These patients with fixed hypertension require a blood pressure around 180 mm. to maintain an adequate renal circulation for the removal of the products of metabolism. The optimum blood pressure is fixed at a higher level than the normal. When the heart fails the kidney decompensates and the patient will develop uremia. I have often demonstrated an increase of the albuminuria and a rise in the nonprotein nitrogen and creatinin of the blood by temporarily lowering the blood pressure with vasodilator drugs. Great care must be exercised to prevent rather than cause a fall in blood pressure in advanced hypertension. Fortunately for the patient the blood pressure is usually fixed at a high level and cannot be lowered even by nitroglycerin or amyl nitrite. When the heart fails from chronic myocardosis, with or without coronary sclerosis and thrombosis, the patient becomes rapidly worse. Hence the heart condition requires careful watching and therapy. Often an accompanying pulmonary emphysema puts an added strain upon the right heart. Acute vascular crises with dangerous sudden rise of blood pressure should be treated with active vasodilator drugs or venesection. The latter may be a life-saving measure in acute right heart failure. The acute vascular crises endanger life by causing cerebral hemorrhage, spasms with cerebral softening, or acute cardiac or renal decompensation.

**Case IV.**—This colored male, age forty-four, was admitted to my service at the Cook County Hospital in October, 1935. The history was obtained from a relative. The patient had been well until six months ago when he complained of severe headaches and attacks of dizziness. He continued to work as a waiter until three weeks ago. He then complained of marked weakness, nausea and vomiting, and drowsiness. At times there was diarrhea. He was brought to the hospital in coma. There was no history of any previous serious illness.

On inspection a whitish powdery deposit was seen on the face, and neck (uremic frost). There were fibrillary twitchings of the muscles of the arms and legs. The reflexes were lively. There was a positive Chvostek sign. The breathing was of the Kussmaul type. The heart was slightly enlarged, measuring  $5\frac{1}{2}$  inches in transverse diameter. The aortic second sound was accentuated. There was a definite pericardial friction rub heard over the entire heart area. There was no evidence of cardiac decompensation. The blood pressure was 275 systolic and 160 diastolic. The urine revealed a specific gravity of 1.012 with albumin, hyaline casts and few red blood cells. The blood chemistry showed a nonprotein nitrogen of 175 and creatinin of 8.5. The eyegrounds revealed a marked hypertensive neuroretinitis.

Because of the short duration of the illness (six months), the very high systolic and diastolic blood pressures, the concentric cardiac hypertrophy, the pericardial friction rub, hypertensive retinitis, high creatinin and nonprotein nitrogen, a definite diagnosis of "malignant" hypertension with uremia was made. To the diagnosis was added uremic pericarditis, and colitis. The necropsy confirmed the diagnosis. The kidneys revealed the picture of a severe malignant nephrosclerosis, with diffuse arteriolosclerosis and necrosis and endarteritis of the arterioles. There was also a uremic pericarditis and enteritis. The heart showed a marked concentric hypertrophy.

#### THE THERAPY OF ESSENTIAL HYPERTENSION

The great variety of therapeutic agents recommended for essential hypertension is the best proof of the unsatisfactory results obtained with most of them. The best result obtainable is to stop the progress of the disease. Much can be done by proper training and conduct to prevent an unfavorable outcome. These patients have a lowered threshold for various stimuli and irritants, which lead to increased vascular tonus. They are very susceptible to psychic influences. Hence psychic therapy is most important of all. These patients require reduced physical activity and mental rest. The benefit of many therapeutic procedures is largely suggestive.

The patient should not become the victim of costly and often worthless medication. We have at present no drug which will bring the condition of the sarcoplasm of the vascular contractile tissues back to a physiologic condition. We have already stated that the cardiac hypertrophy is compensatory and necessary in overcoming the increased peripheral resistance and stasis.

There are two means of reducing the blood pressure: (1) by action on the heart, and (2) by action on the arteries and arterioles. Any agent which affects only one of these factors must endanger the functional capacity of the other. The ideal drug should affect both at the same time, and gradually, not suddenly. We therefore attempt to relieve the heart and at the same time relax the peripheral vessels. Relief of cardiac tension is accomplished by venesection. But this is indicated only in moments of danger, such as pressor vascular crises with acute insufficiency of the heart and pulmonary edema, or marked rise of pressure in cerebral hemorrhage. The effect is of short duration.

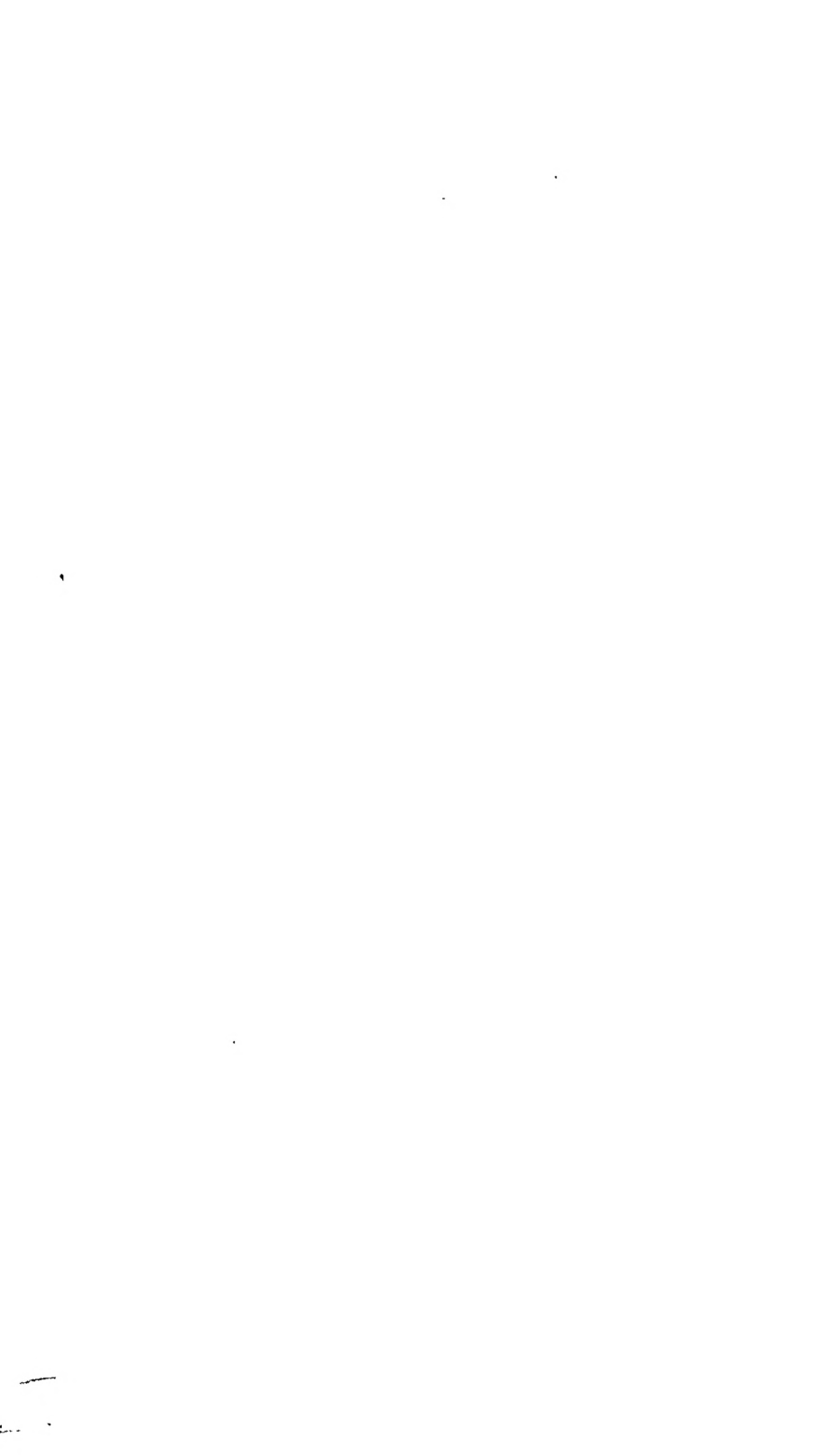
Of the drugs sedatives act best by influencing the vasomotor center and lowering vascular tonus. The vasodilators, such as amyl nitrite, nitroglycerin, erythrol tetranitrate, sodium nitrite, etc., are indicated in angina pectoris, cardiac asthma, cerebral vascular spasms, and marked rises of blood pressure. Papaverine and its derivatives are advised by Pal. The xanthin compounds are of value, as they act on the coronary, cerebral, and renal vessels. As a rule they do not cause much drop in blood pressure. Caffeine, theobromine, theophylline, diuretin, theominal, and aminophyllin are the most popular. Their chief value is the dilation of the coronary arteries, also the cerebral vessels.

The diet should be sufficient to maintain the weight at a normal level. A mixed diet of 1500 to 2000 calories is enough. Albumin, purine foods, and salt should be restricted. Fluids should be limited to an average of 1500 cc. daily. There is no evidence that a moderate protein intake has any harmful effect in essential hypertension.



Carefully dosed exercise is beneficial especially for the lazy or obese hypertensive. Proper exercise produces a more economic metabolism and tends to reduce the blood pressure especially in obesity and diabetes. Walking, riding and golf are most suitable. They improve respiration and cardiac activity. Massage is less valuable than carefully controlled active exercise. Baths at 35° to 40° C. reduce blood pressure, those over 40° C. raise the pressure. Warm or lukewarm baths are best. Warm foot baths are very useful in cerebral congestion. Hot turkish baths should be forbidden. Carbon dioxide baths are beneficial with blood pressures below 200. A warm climate and moderate altitude are most favorable. Mild laxatives such as Carlsbad salts, or other saline laxative, are of value.

Finally, a restful régime with reduced physical and mental strain, plenty of rest periods, and at least eight to ten hours of sleep, is the best remedy. Bromides, amytal, or other sedative may be required from time to time. Tobacco should be forbidden or reduced to a small amount. We do not have time to discuss the therapy of the decompensated heart, cerebral hemorrhage, or renal insufficiency.



## CLINIC OF DR. WILLIAM A. BRAMS

CARDIOVASCULAR DEPARTMENT, MICHAEL REESE HOSPITAL

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### OCCULT HEART DISEASE

THERE are cases of heart disease in which the clinical manifestations are so obscure or so atypical that *an underlying cardiac factor is not suspected* as being the cause of the patient's symptoms. Such patients may be said to have occult heart disease because the cardiac factor is obscure. The term is not to be employed as a designation for various congenital or acquired cardiac defects which produce no symptoms nor in connection with the well-recognized fact that the degree of anatomical change frequently is not parallel with the severity of the symptoms. The significance of the term will, perhaps, be appreciated best by the presentation of the illustrative cases of which the following are examples:

The first patient to be discussed was admitted to the hospital several weeks ago. He was a colored preacher fifty-two years of age who complained of severe pain in the left foot three days before admission. The pain became more intense, began to ascend to the leg and involved the opposite foot two days after his symptoms began. There were no other complaints at the time, and there was nothing in the past history which could throw light on the cause of the increasingly severe pain in the feet and left leg. He had been active in his work, was not short of breath and never experienced thoracic discomfort, nor was he aware of any other symptoms which might attract attention to his heart.

Examination revealed a well-nourished, apparently middle-aged colored adult who was obviously in great pain. The left foot showed evidences of dry gangrene, the toes were cold and no pulse could be felt in the lower extremity. The right foot was not gangrenous but was cold and no pulse was palpable in

this limb. There were a few crepitant râles at the right base of the lungs and the apex beat of the heart was slightly beyond the midclavicular line. The heart sounds were regular, of good quality and no murmurs were audible. Systolic blood pressure was 165 mm. mercury and the diastolic was 105 mm. Nothing abnormal was found in the abdomen. The pupils were sluggish to light but the patient had received morphine for pain. The knee jerks could not be elicited. The patient was too ill to be moved for further study and a tentative diagnosis of hypertension with atherosclerosis was made with probable obliterative disease in the vessels of the lower extremities due to thrombosis. Conservative measures were employed while waiting for a line of demarcation to form. Gangrene rapidly extended until both feet and legs and the lower half of the thighs were involved. The patient rapidly became severely toxic and died a few days later and before surgical measures could be employed.

Autopsy revealed embolic occlusion of both tibial arteries with extension downward by thrombosis and a more recent riding embolus was found at the bifurcation of the abdominal aorta. The heart was moderately enlarged and showed an old occlusion of the anterior descending branch of the left coronary artery with large aneurysm formation of the left ventricular wall near the apex. A large mural thrombus filled the inner aspect of this aneurysm in the left ventricle. The thrombus material was soft and presented several pedunculated areas some of which had apparently broken off and were carried by the blood stream as emboli to the lower extremities. There were no other abnormal findings except moderate congestion of the lungs and no other possible source for the emboli could be found.

Here is a classical example of so-called "occult heart disease" which produced no cardiac manifestations but resulted in fatal complications. Careful questioning during life failed to elicit any history suggestive of coronary occlusion or cardiac failure and physical examination revealed very little evidence of heart disease except slight cardiac enlargement. This is not

as rare as is ordinarily supposed and it is common knowledge that healed myocardial infarcts and occlusion of the coronary arteries are not infrequently found at autopsy without symptoms having developed during life. Parallel situations are seen in the finding at autopsy of gallstones or peptic ulcer without symptoms having been present during life to disclose the existence of such lesions. It may be worth while to mention again that coronary occlusion may exist without symptoms or it may produce a variety of clinical pictures not all of which are characteristic. The presence of a healed myocardial infarct as an accidental finding at autopsy may furnish the evidence that such a condition existed without symptoms during life. Sudden death without previous warning in a patient who has never experienced precordial pain is another form in which coronary occlusion may manifest itself. The third group produces the classical picture of substernal or precordial pain, vascular collapse, fever, leukocytosis and the distinctive electrocardiographic changes. There is still another group in which abrupt dyspnea is the first and only sign; no pain being present at any time. There is a rather large number of patients with coronary occlusion in whom gradual cardiac failure progresses and in whom severe pain or dyspnea are not very evident at the onset. Finally, there is a rarer form in which few or no manifestations appear until embolic phenomena occur as the only evidence of the existing myocardial infarct. Our patient is an example of this last form and the condition should be kept in mind in the differential diagnosis of embolic phenomena when the source of the embolus is obscure.

The second example is that of a physician sixty-three years of age who complained of pain in the epigastrium with some radiation to the right side of the abdomen and upward to the chest. The attacks began about two years before admission to the hospital and consisted of severe pain in the region indicated together with nausea, occasional vomiting, and marked weakness. The duration of these symptoms was from a few minutes to several hours and usually left the patient much fatigued and shaken. Jaundice was never observed and fever

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was absent but definite tenderness in the right upper quadrant of the abdomen was a frequent finding. A diagnosis of cholecystitis with probable gallstone colic was made by his physician and surgical treatment was advised. Roentgenological examination did not reveal any abnormality in the gastro-intestinal tract. Cholecystography furnished no decisive information and plain films of the gallbladder failed to disclose evidence of disease of the biliary tract. The patient wished to remain on medical management for a while and decided to go to the west coast for a vacation. He made the trip in a leisurely manner and observed with satisfaction that his symptoms improved. While sojourning at a high altitude he decided to do some mountain climbing, a sport in which he engaged for several days. The pain in the upper abdomen became much worse abruptly and persisted for two days. Hypodermic injections of morphine were required to induce some degree of comfort. Dyspnea and collapse now became evident. His blood pressure fell from the usual level of 140 mm. mercury to 94 mm. and an easily recognizable picture of coronary insufficiency was now apparent. An electrocardiogram was not available at the time but the patient remained in bed for eight weeks during which time he was treated as a case of coronary occlusion. He subsequently returned to his home but cardiac failure was now evident and attacks of pain recurred at irregular intervals until sudden death ten months later.

Autopsy revealed a fresh occlusion of the anterior descending branch of the left coronary artery and several old occlusions in both the right and left coronary arteries. The liver showed evidence of moderate fibrosis and chronic passive congestion but the gallbladder and biliary passages were normal.

It is a question, of course, whether electrocardiographic studies at the onset of the symptoms would have revealed the true nature of his illness. The accuracy of this diagnostic procedure has been increased with the introduction of the fourth lead but we have seen patients with anatomical occlusion of the coronary artery in whom careful electrocardiographic studies sometimes failed to show evidence of this condition.



It is possible that more careful questioning of the patient would have revealed the information that the abdominal pain also radiated under the sternum as well as elsewhere to the chest. Also, that some degree of thoracic oppression occurred or that dyspnea was experienced during the attack. It would be of interest to know if the upper abdominal tenderness was circumscribed or whether it was diffuse over the entire liver region as one would expect in acute attacks of passive congestion of the liver. The occurrence of abdominal pain in cardiac disease also brings up the question whether some of the cases of so-called "abdominal angina" are actually due to atherosclerosis of the mesenteric arteries even if they were found at autopsy to be involved in a high degree. The fact that the abdominal symptoms completely dominated the clinical picture in this case of coronary disease is an example of the care necessary in excluding obscure clinical pictures of coronary disease in patients past middle age.

The diagnostic difficulties are, of course, increased when gallbladder pathology coexists with coronary disease. One must then weigh the part played by each and also whether surgical removal of the biliary tract disease can be undertaken with safety because very gratifying results have been obtained by such a procedure. Surgical treatment in such instances has resulted not only in amelioration of abdominal symptoms, but the cardiac difficulties have also frequently been greatly improved.

Time and space prevents us from presenting further cases of so-called "occult heart disease." It is not our intention merely to coin a new phrase for an old conception. Our purpose is to remind the physician that heart disease can masquerade as some other illness, that there may be no obvious cardiac manifestations until a very exhaustive study is made from the cardiovascular standpoint and that such conditions will be recognized more frequently if such possibilities are kept in mind. There is a great deal of truth in the axiom that we diagnose the conditions we think of and miss those which are not taken into consideration while deliberating on a differential diagnosis.



## CLINIC OF DR. CLEVELAND J. WHITE

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### TREATMENT OF CHRONIC LEG ULCERS

ULCERS of the extremities often present a difficult problem for diagnosis and hence the proper therapy. The recent literature has been quite full of new forms of treatment for various types of ulcers. The dermatologist is often consulted in regard to diagnosis while many of the therapeutic procedures are distinctly in the realm of the surgeon and better handled by surgical methods.

#### VARICOSE ULCERS

One of the most common types and one which gives considerable trouble in treatment is the ordinary varicose ulcer and its complications. The clinical picture of varicose ulcer is very well known. The location is usually on the lower half of the legs at the inner aspect and above the malleolus. The ulcer is usually single and usually surrounded by lichenified callous border. The uncomplicated varicose ulcer is best handled by applying an Unna boot. All are acquainted with this type of boot, and I just wish to emphasize it in stating that it is still our best method of treatment, by giving rest to the area of the ulcer in order to bring about healing. After healing has taken place the obliteration of the varicosities is in order.

Since the injection method has come into vogue, surgical removal has practically vanished as a method of therapy in the ordinary case. The type of fluid used in injection varies in the different clinics, but it has simmered down pretty well to potassium oleate, sodium morrhuate, glucose, quinine, urethane,

sodium salicylate and sodium chloride. Different statistics are given for the various types of injection, but the main indication for success in these varicosities is proper technic, with the proper selection of suitable cases. De Takáts uses potassium oleate in 5 and 10 per cent strength, and reports excellent success in a large percentage of cases. Some of the large clinics use elastic plaster in place of the Unna boot. Douglas has



Fig. 12.—Varicose ulcer.

recently reported his results and believes that it answers the purpose very well. In some 90 cases he got prompt healing in almost 97 per cent. Whether the Unna boot or the elastic plaster will be used depends upon the individual's skill in handling the method.

The complications of the injection method of treating varicose veins are well known and have to be considered in using this method. The three most common complications are

phlebitis, thrombosis, and thrombophlebitis, which Zimmerman has discussed in detail.

Ulcers of the extremities associated with varicosities which are found below the malleolus are oftentimes due to failure of the deep saphenous vein. Here de Takáts has been foremost in advocating the ligation of the vein in order to produce a healing in this stubborn type of ulcer.

It hardly needs to be reiterated that in varicose ulcers associated with superficial infectious dermatoses, either bacterial or fungus, it is necessary to use applications to cure the dermatological features before active measures are taken to heal the ulcer.

#### PHAGEDENIC ULCERATIONS

Another type of ulceration which has been attracting more and more interest not only because of its rarity but because of its stubbornness in yielding to treatment is the so-called "phagedenic ulcer." This type is apparently becoming more common. After a minor infection, as on a toe, or after drainage of an abscess, as of one of the inguinal lymph nodes, there occurs a slow but insidiously progressive destruction of the skin. It has been a baffling problem because none of the usual bactericidal agents, either chemical or physical, seems to exert the slightest influence on this infection. It is characterized by remarkable chronicity, and until its final stages it is usually not attended by severe constitutional symptoms. However, since Cullen has emphasized the value of the cautery and Baer's application of maggots in this type of infection, a satisfactory method of treatment has been evolved in most cases.

Holman of the Department of Surgery of Stanford University has analyzed several cases in which the method of treatment is very instructive. In one of his cases an axillary abscess followed a small blister of the left hand which had been opened and exposed to animal fertilizer. In the original culture only hemolytic streptococcus was recovered, but after eleven months of steady progression and secondary ulcerations of the chest, *Staphylococcus aureus* was recovered in culture as well as the other organisms. In this particular case no response to

therapy was had until the maggot treatment was used. The combination of these two organisms has been emphasized by Meleney in various writings. Meleney designates this disease process as a result of a bacterial synergism and believes a synergistic bacteriology of certain types of bacteria causes this progressive gangrene of the skin. Cases involving especially the inguinal region demand an early recognition of the irresistible character of this type of infection, and even bold surgical excision of the overhanging edges occurring during the infection to prevent involvement of the large blood vessels.

Holman cites another case of trivial injury of the fingers followed by extensive abscess of the axilla which had progressed for nine months' time. Finally streptococci and anaerobic staphylococci were recovered, whereupon he instituted extensive and thorough cautery *débridement* and maggot treatment in addition to blood transfusion and high vitamin diet.

#### TRAUMATIC AND ANEMIC ULCERS

Ulcers which occur after trauma at times present a very difficult situation. Rest and various other measures have been used, together with different applications. The use of sulphydryl, containing the amino-acid cysteine has been used by Brunsting and Simonsen with marked success in this type of case. Others have used cod liver oil as wet dressings.

Recently R. A. Jacobson has been using ordinary sterile vaselin with the ulcer completely covered with the Unna boot, following Orr's method of treatment of osteomyelitis, with success. Saylor and others have used acetylbetamethylcholine chloride iontophoresis in the treatment of chronic ulcer especially the varicose type.

#### ULCERATIONS IN PERIPHERAL VASCULAR DISEASES

Ulcers of the extremities occur in the chronic peripheral circulatory diseases. It is important to differentiate between the functional and organic types.

**Functional.**—Vasomotor disturbances consist of a vasoconstrictor and a vasodilator nature. Raynaud's disease is an

example of the vasoconstrictor disorder and erythemomyalgia, of the vascular spasm type. This latter type never ulcerates. In the second group organic insufficiency is due to the occlusion or diminution of the lumen of the blood vessels. In this group thrombo-angiitis obliterans or Buerger's disease and arteriosclerotic endarteritis obliterans are two important clinical divisions. In this organic group pulsations of the peripheral vessels are diminished or absent. These are the dorsalis pedis and posterior popliteal in the leg and foot. When pulsation in



FIG. 13.—Thrombo-angiitis obliterans (Buerger's disease).

the main vessels is absent or diminished the extremity becomes red in color when dependent and naturally blanched with elevation. Trophic changes followed by gangrene usually occur unless the various types of treatment are instituted. In the case of thrombo-angiitis obliterans immediately preceding or following trophic changes, the pain is continuous and excruciating and in the past amputation has been necessary for relief. In the arterio-sclerotic group pain is not a very prominent feature and there is no associated, recurrent superficial phlebitis

as in thrombo-angiitis obliterans. While so-called "Buerger's disease" has been mainly found in the Jewish race and in the male sex, there are now ample statistics to show that it occurs in other races, and in the female sex. In the arteriosclerotic type x-rays of the extremities will show calcareous deposits in the blood vessels. The disease usually occurs after the age of fifty-five, whereas thrombo-angiitis obliterans usually occurs between the ages of seventeen and fifty.

A great deal of interest has been shown in the treatment of Raynaud's disease in the past few years by the institution



Fig. 14.—Endarteritis obliterans. Woman, aged seventy-two, with ulceration of nine months' duration. The peripheral circulation is occluded, and the extremity cold and clammy.

of surgical methods, namely, periarterial sympathectomy. Which has led to sympathetic ganglionectomy to secure the best results. Most clinicians agree that the essential vascular disturbance in Raynaud's disease is arterial spasm. However, there is some disagreement as to which types of cases should be subjected to sympathectomy. The recent work by Crisler and Horton on the effect of fever on the digits has been used to differentiate between thrombo-endarteritis obliterans and Raynaud's disease. About one third of the patients with thrombo-endarteritis obliterans had color changes, red, white



and blue, which indicated vasospastic disorder. However, these workers feel that the vasospasm which gives rise to the color changes is secondary to or superimposed upon an organic occlusive disease of the arteries. Their work emphasizes the primarity of organic changes in thrombo-endarteritis obliterans and of functional changes in Raynaud's disease. Until the advent of periarterial sympathectomy the treatment of Raynaud's disease has been very ineffective. The use of this surgical procedure should be seriously considered to avoid the advanced gangrenous stage.

In the treatment of thrombo-endarteritis obliterans all clinicians advise conservative measures. Silbert, of New York, has had excellent results with the use of hypertonic salt solution intravenously. He has recently reported a large series of cases which emphasize the successful results following the use of this conservative measure. The diagnosis of a situation of this type and treatment will prevent the cases that used to go on to amputation, which is a serious economic handicap in this group of usually young men. Sodium citrate has been used by other workers. Other methods have as their basis the increase of the peripheral circulation, such as the postural exercises of Buerger, the application of dry heat, and the cessation of tobacco in every form. In an excellent critical review of the recent literature on surgical treatment of peripheral vascular disease, Scupham and de Takáts feel that sympathectomy in patients with Buerger's disease is best limited to the upper extremities when digital gangrene and intractable pain are present. This is based on the premise that relief from pain in the extremities, excluding amputation, can be obtained by other measures. In patients in the forties paravertebral alcoholic injections are occasionally of benefit.

The treatment of the arteriosclerotic group has not been so successful. While the occasional case is associated with diabetes, syphilis, lead poisoning, etc., usually no such etiology is discovered, and general arteriosclerotic measures have to be used. Recently mechanical improvement of the circulation by passive vascular exercises has been of material assistance in

these types of cases. In a recent monograph on passive vascular exercises, Louis G. Herrmann emphasizes the value of conservative management of obliterative arterial diseases of the extremities. When gangrene appears, then amputation is necessary, whereas in thrombo-angiitis obliterans amputation is now becoming rarer (9 per cent in Silbert's series). De Takáts emphasizes that in cases of diabetic gangrene an important distinction has to be made between the condition that is primarily due to deficient circulation and that which is primarily due to infection. Naturally both conditions may be present. While the former demands a major amputation, the latter is solved by minor amputation or sufficient drainage. In the gangrenous state of older patients, especially in those with diabetes, conservatism must not lead to unnecessary delay in facing inevitable amputation. Tests are quite accurate now to determine the collateral circulation to ascertain the level for amputation. In a woman of seventy-two, who was recently observed, the ulceration appeared just at the distal extremity of the small toe of the left foot. Early recognition and conservative management usually will save the extremity from amputation.

#### ULCERS DUE TO INFECTIONS

Infectious ulcers of the extremities are quite well known. The ordinary superficial fungus infection (ringworm) with secondary infection can cause an ulcer, especially where there are organic peripheral circulatory disturbances. Several of this type of case have been observed. In these, sodium citrate treatments have been used intravenously to help to increase the circulation, while local fungicidal preparations are used as local applications.

Ulcers of late syphilis can occur on any part of the extremities, but more often at the sites of trauma, for example, of the knees. Clinically, the findings have been those of ulcerating gumma; the clinical stages have been emphasized again and again by Stokes. His 10 salient features of diagnosis of late syphilis are present in one form or other. He emphasizes the solitary character, the asymmetry, the indurated infiltra-

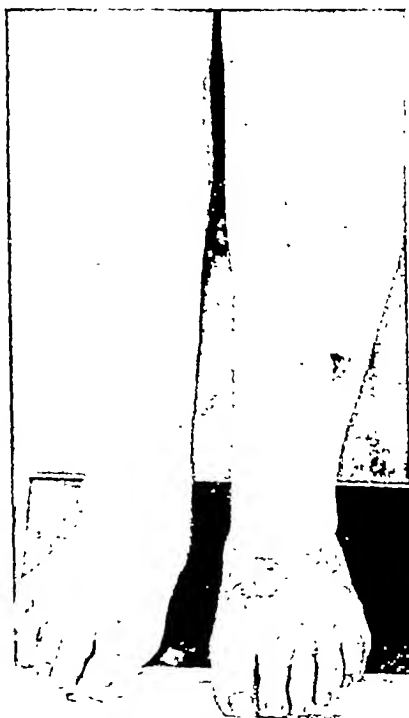


Fig. 15—Epidermomycosis ("ringworm") of foot with secondary infection and ulceration of leg.

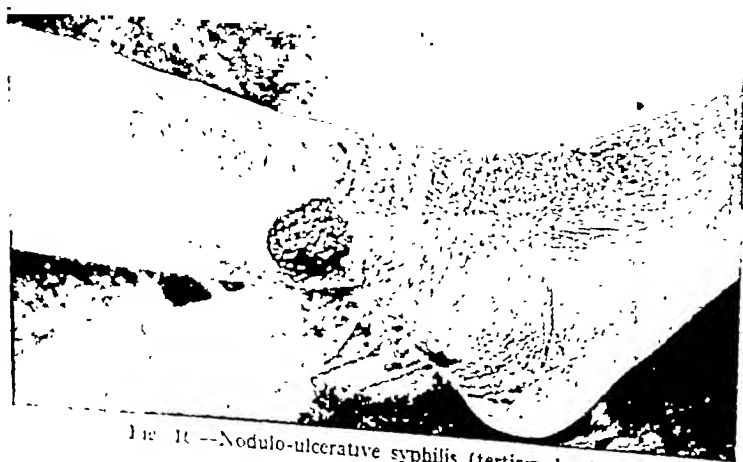


Fig. 16—Nodulo-ulcerative syphilis (tertiary lues).

tion the indolence, the arciform configuration, sharp margins, tissue destruction, peripheral extension and superficial

atrophic scarring with peripheral hyperpigmentation. While the serology is usually positive to support the clinical diagnosis of nodular or ulcerative syphilides, the clinical characteristics are usually so apparent that the serology is only confirmatory. Occasionally the ulcerating gummatous area will be accompanied by a satellite lymphangitis, as observed in Stokes' clinic several years ago. Furthermore, with secondary infection the patient may have definite fever of intermittent character.



Fig. 17.—Mal perforans. Woman, forty-two years of age, with positive blood and spinal fluid serology, with neurological findings of tabes dorsalis and ulcerations of fifteen months' duration.

Ulcers of the extremities due to tuberculosis are usually of 2 types, either a primary inoculation of tuberculosis following injury or ulcers of the calves of the legs, called erythema induratum. At the onset, a tuberculous ulcer is manifested by one or several ulcers of dusky red color which become lighter when the ulcers have a jagged border. Histological section of a border of a tuberculous ulcer is the typical histology of tuberculosis and is easily recognized. If a tuberculous ulcer heals the scar is thickened and hypertrophic as compared with the thin, atrophic cigarette paper scar of a late syphilide. The

treatment of tuberculosis of the skin has taken on additional interest since the institution of dietary measures, especially those suggested by Gerson of low starch and low salt. Other workers have made minor modifications and the results have been striking in numerous cases.

Erythema induratum is manifested on the posterior portion of the legs by bluish-red nodules followed by ulceration. They are of a symmetrical character and oftentimes come in showers. While histological section will not show a typical tuberculous nature, sufficient clinical studies have been carried through which substantiate the tuberculous origin from some focus in the body, either visceral or glandular. Direct proofs by guinea-



Fig 18.—Erythema induratum (a tuberculous entity).

pig inoculation have been found by several workers. It usually occurs in youthful individuals, especially in young girls. Such a patient was recently observed: she felt that an industrial injury was the cause but there was no basis for such a supposition.

Ulcers of deep invading fungi are well known. The ulcers of blastomycosis have characteristic pinpoint abscesses in the ulcer border. Actinomycosis does not occur on the extremities very often. This diagnosis is substantiated by finding actinomycetes in the purulent discharge of the draining abscess.

Maduromycosis, which is manifested by large nodules which become purulent and have a discharge of small seedlike growths of both black and white color, is another form of ulcer.

So-called "Madura foot" is very uncommon in the United States, though a recent case has been reported by K. L. Puestow.

Sporotrichosis seldom occurs on the lower extremities, as the initial lesion is practically always traumatic on the digits, forming a sporotrichotic chancre with a cordlike lymphangitis extending to the extremities. The rare constricting ulcer of the toe, so-called *ainhum*, practically never occurs in this country. It is a constricting band which gradually causes ulceration and amputation of the digit.

#### MALIGNANT ULCERS

The occurrence of ulcers by malignant growth is, I believe, becoming more common, especially those of the pigmented mole type. The ordinary basal-cell epithelioma with a pearly border and central ulceration and peripheral growth (the so-called "rodent ulcer") very seldom occurs on the lower extremities. Squamous-cell epitheliomas occur following injuries, and at times are primary growths. Here the ulcer is deep seated, the border advances rapidly, and soon there is invasion of the adjacent lymph nodes by metastases. The squamobasal cell type, which histologic picture has recently been emphasized by Montgomery, has usually been found on the trunk. A diagnosis of squamous-cell epithelioma with confirmation of the clinical findings by histologic section should be dealt with by drastic surgery. Electrosurgical removal is the treatment of choice for both the basal and squamous-celled type; radium can be used in the older patients. In a thorough study of 61 cases of squamous-cell epithelioma of the extremities, DeBere and Stevenson found that metastases to regional lymph nodes occurred only in the large growths, usually larger than 3 cm. in diameter.

The occurrence of pigmented moles, especially the bluish-black type, is often seen, especially on the toes. No etiologic information can be ascertained in the average case, the bluish mole appearing in conical form and growing in a site that is subject to irritation. Conservative dermatologists recommend

radium if the lesion is not too large—not over a  $\frac{1}{4}$  of an inch in diameter—because surgical excision is unsatisfactory due to the possibility of melanoblasts being found inches away from the original lesion. Surgical interference in such a predicament may lead to rapid dissemination. In several cases, however, radium has had no effect even in large doses, and surgery was necessary in competent hands, with excellent results. The occasional occurrence of sarcoma calls for histologic study of normal growth in order to detect malignancies in their incipency. A case was recently observed in the practice of Dr. C. W. Yarrington where extensive melanocarcinoma were present and no primary lesion could be determined.

#### X-RAY BURNS

Ulcers produced by excessive x-ray treatment are only too common. One of the most extensively involved cases is that of a young woman who had x-ray treatment in a so-called “hair-removal” institute for hypertrichosis of the lower extremities. Here the large ulcers of the legs were accompanied by severe and intense pain. The indicated treatment is that of skin transplants by surgical methods.

Some hope has been given recently in small x-ray burns by using aloe vera in 50 per cent ointment which in many instances encourages epithelialization, decreases the pain and allows the small ulcer to heal. The use of the ointment is much more satisfactory than the aloe vera leaf which was first advocated. Ulcers from radium, like those from x-ray, can be prevented when the radium is used with ordinary skill.

#### EXTRAGENITAL VENEREAL ULCERATIONS

Veneraeal ulcers as chancroid, granuloma inguinale and lymphogranulomatosis of Nicolas and Farre can occur on the extremities, especially the chancroid type. These ulcers have a soft base, are usually multiple, and at times are distinctly difficult therapeutic problems. Actual cauterization has been advocated and in some cases it is necessary to use tartar emetic intravenously to procure results. Lymphogranulomatous lesions usually are associated with strictures around the rectum.

Here the diagnosis may be confirmed by a positive Frei test. Beginning with a nodule on the glabrous skin, the granuloma inguinale lesions spread in the form of an ulcerative granular patch. The borders are distinct and the surface is riddled with papillomatous elevations. The center gradually becomes cicatrized.

#### FACTITIAL ULCERS

Ulcers produced by the patient either because of mental derangement or for the purpose of creating sympathy or increasing compensation must be kept in mind. Their annular and geometric configuration usually betray their origin, even if it is difficult to discover any trace of the material used. A young woman of twenty-two, recently observed, had a deep-seated ulcer of the extremity and one in an appendectomy wound of the abdomen. The occurrence of lesions on the body, especially ones she was able to produce with the right hand, finally proved the origin of these multiple ulcerations. While such ulcers have been described, it is rare to see such a lesion on the abdomen reaching practically to the peritoneum. In this case it was produced by phenol. The patient was able to disengage in the practice after the true cause was related to her. In patients with mental aberrations, it becomes a case for psychiatric treatment.

#### MISCELLANEOUS

Ulcers of the extremities, associated with general conditions, are quite well known, the most common being in the sickle cell anemia. They occasionally occur in multiple sclerosis and as a sequel of encephalitis. Even ulcers following typhoid and preceded by arteritis have been reported. Garvin and Trumess have reported ulcers due to localized allergy.

Ulcers and granulomatous lesions following the ingestion of halogen salts, such as iodides and bromides, are characterized by a vegetative appearance and the history of the ingestion of such medicament. Some cases occur after taking bromo-seltzer in which the victim is not aware that bromide is being taken.



Ulcerations occurring in the malignant lymphoblastoma group, as granuloma fungoides, the leukemias and Hodgkin's disease, are usually diagnosed by other corroborative clinical findings and microscopical studies.

Ulcerations occur on the feet and lower extremities due to industrial pursuits. Such have been reported in workers due to chrome and lime, fumes of hydrochloric acid and hydrofluoric acid and shale oil.



## CLINIC OF DR. LUKE W. HUNT

ALBERT MERRITT BILLINGS HOSPITAL

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### THE DIAGNOSIS AND TREATMENT OF FIBROSITIS AND MYOSITIS

#### FIBROSITIS

FIBROSITIS is an inflammation of white fibrous tissue and may, therefore, occur in many parts of the body—in fascia, aponeurosis, sheaths of muscles and nerves, tendons and ligaments, articular capsule, periosteum and subcutaneous tissue or any part where fibrous tissue is found. Although widely recognized abroad, fibrositis has received but scant attention in this country, and many American monographs on rheumatic diseases fail to mention it or devote very little attention to the condition. Nevertheless fibrositis is common, and is responsible for many painful conditions often termed myalgia, muscular rheumatism, neuritis and so forth. To designate the involvement of special parts certain terms are employed, synovitis, tenosynovitis, bursitis, and perineuritis, etc. The two most common forms are the intramuscular and the periarticular. The former may be localized as in lumbago, torticollis and pleurodynia or diffuse as in generalized muscular rheumatism. Periarticular fibrositis may affect the capsule of the large joints or many small joints. In any of these situations it is usually acute at first, but may become subacute or chronic, the last being more common in later life.

**Etiology.**—The essential cause of fibrositis is infection in the great majority of cases, and usually from a local focus. Many investigators believe streptococci responsible while others incriminate unidentified or other toxins. English writers believe that under certain conditions of irritation the fibrositis nodule introduces toxic material into the circulation when the

original focus of infection has long been removed, and that it has itself become a focus, secondary to the infecting focus but needing no reinforcement for its effective existence. Trauma, muscular strain and exposure to cold and damp are predisposing factors, especially in acute attacks. Prolonged strain on tendons and ligaments may be responsible for a chronic fibrositis but infection is often superimposed. It may follow exposure to a draught of air or sudden chilling after heavy exertion may bring on an attack. One attack renders an individual more liable to subsequent attacks. Individuals with gout seem prone to fibrositis. Chronic alcoholism or lead poisoning may be etiological factors.

**Pathology.**—The essential pathological characteristics of fibrositis are a diffuse and localized inflammatory hyperplasia of fibrous tissue. The localized lesions may be palpable as nodular tender regions of infiltration in muscles or near the attachment of tendons. In acute cases there is a serous exudation in the affected parts, and following this there may be proliferation of the fibrous tissue. This may extend between the muscles and cause stiffness and pain. Disability with muscular atrophy may result.

**Symptoms.**—The symptoms and physical findings, and method of arriving at a diagnosis are illustrated by this patient, a forty-one-year-old male, a plumber, who came to the clinic complaining of pain in the lower part of the back of three weeks' duration. He had enjoyed good health all his life except for a similar attack which lasted for two weeks about six months ago. The night before the present attack the patient played hand-ball and perspired freely. He does not remember that he injured his back at that time. The next morning he awoke with pain and stiffness in the lumbar region. The pain was a dull ache but became sharp and severe when he stooped or turned his body. It did not radiate. There is no history of a cold or sore throat before the onset. He remained in bed. applied heat with slight relief but the condition has persisted. He does not think he has had a fever.

The past history, family history and inquiry by systems

are essentially negative. Upon physical examination we find this patient to be a well developed and nourished muscular individual who does not appear acutely ill. The temperature is 99.2° F. The pupils are equal, regular, and react to light and accommodation. There is no lid-lag or exophthalmos. There is no discharge from the nose, and no pain over the sinuses. There is no discharge from the ears, the drums are normal. The tongue protrudes in the midline, there is no tremor. The teeth show a good deal of dental workcrowns and large fillings. There is retraction of the gums around the crowns. There is no lead line. The tonsils are out, the pharynx is not injected and there is no postnasal drip. The thyroid is not enlarged, there are palpable, tender anterior cervical glands on the left. The lungs are clear to auscultation and percussion. The heart border is 9 cm. from the midsternal line. There is a soft systolic murmur at the apex, not transmitted.  $P_2 > A_2$ . The blood pressure is 130/80. The abdomen is flat. There is no tenderness or masses. The liver, kidneys and spleen are not felt. There is no hernia. The knee jerks, triceps, biceps, Achilles reflexes are present and equal. There is no ankle or patellar clonus. Romberg is negative. Flexion of the thigh on the abdomen and extension of the leg causes pain in the lumbar region. There is no tenderness over the sacro-iliac joints. When the thigh and knee are flexed and the external malleolus is placed above the patella of the opposite leg, depression of the knee causes no pain in either hip. There is tenderness of the lumbar muscles on both sides. Tender areas are found just above the iliac crests and lateral to the spine but no definite nodules are felt. The patient has difficulty in turning on his side and cannot assume a sitting position unless he is assisted. There is no scoliosis. There is no tenderness to pressure or percussion over the spinal processes. The arches of the feet are normal. Rectal examination reveals good sphincter tone, the prostate is smooth, firm, not enlarged but slightly tender. The seminal vesicles are not tender. Pressure on the sacrum and coccyx causes no pain. The Wassermann and Kahn tests are negative. The leukocyte count is 10,700,

hemoglobin 88, red blood cell count 5,250,000, urine specific gravity 1.015, no albumin, no sugar, occasional leukocyte. Microscopical examination of the prostatic fluid shows an occasional leukocyte. x-Rays of the pelvis and lumbar spine are normal. x-Rays of the teeth show two lower molars on the left with periapical lesions, and a right upper molar with incomplete root canal therapy.

From the history, symptoms, physical findings, laboratory examination and x-ray findings it is very likely that this patient has an acute fibrositis of the lumbar muscles. The predisposing factors are probably an injury and exposure to a draught, and superimposed is a dental infection.

**Diagnosis.**—In attempting to arrive at a diagnosis of a patient with such symptoms one can usually detect those cases that are due to a systemic disease by observing that the patient not only complains of pain but looks acutely ill. If he does so, and his temperature is 100° F. or higher, it is quite likely that one is dealing with a systemic condition at its onset or perhaps it may be a meningitis, an acute myelitis or even an acute rheumatic process, and in all of these, the pain in the back is only an obstrusive symptom to which will be added some of the signs distinctive of the disease. Often, however, as in this case one has to deal with a patient who, except for the pain in the back, is comparatively well. In such cases it is advisable to ask the patient how it arose—for example: did it follow a blow or some unusual exertion or unintentional movement? Then the duration, if it is constant or intermittent, and if it radiates. Inspection may reveal a skin condition such as herpes, swelling or redness or undue prominence of a spinal process, bruises or purpura or atrophy of muscles may be apparent. Inspection may also reveal any abnormality of the spine. Palpation may reveal tenderness on pressure of muscle or bone, it may show fluctuation, hyperesthesia of the skin or fibrositic nodules or cords. The next step is to test for disease of the bone by tapping each spinal process with a percussion hammer, jar the heels alternately with the legs held rigid, and note whether pain is elicited. Then one may find if pain is

caused by movements of any kind—flexion, extension, abduction, adduction and rotation. Careful examination of the abdomen for tenderness or masses, and lastly x-ray examination of the painful area should be done. Careful search for foci of infection should be made. By such an examination an etiological diagnosis can often be made.

**Differential Diagnosis.**—Other forms of fibrositis which are likely to be acute at the onset are torticollis and pleurodynia. Pain and stiffness of the neck occur in a number of different diseases and the significance may be grave or trivial. It is not right to assume that the condition is trivial without a thorough investigation. When due to fibrositis it usually affects the muscles of the anterolateral or back region of the neck, is most often unilateral and occurs most frequently in the young. The patient holds the head in a peculiar manner turned to one side, and rotates the whole body when attempting to turn it. Exposure to cold or sleeping in a cramped position may give rise to a transient stiff neck associated with no other symptoms. Often in such cases there is a history of the patient waking up in the morning with a stiff neck, and frequently one will find a latent focus of infection in the teeth, throat or sinuses. The affection of the muscles of the head and neck may be associated with headache, the so-called “indurative” headache.

Pleurodynia involves the intercostal muscles on one side, and in some instances the pectorals and serratus magnus. This is a very painful form of the disease as the chest cannot be at rest. A deep breath or coughing causes pain, sometimes over a limited area. Tenderness of the affected muscles may be the only physical sign present, and it is important that graver mischief such as pleurisy, pneumonia or aortic aneurysm be excluded before a diagnosis of pleurodynia is made. It may be difficult to distinguish from intercostal neuralgia in which the pain is more circumscribed and paroxysmal, and there are tender spots along the course of the nerves. It is well to remember that fibrositis nodules in the left sixth interspace may give rise to pain described as under the heart which may be

mistaken for cardiac pain. Fibrositis in the right axilla in the fifth to seventh interspaces may cause epigastric pain simulating that of duodenal ulcer, and fibrositis nodules in the interspaces from the eighth to the eleventh may cause attacks of pain felt over the abdomen which may be mistaken by the physician or by the patient for pain arising in the colon or in the appendix. In the latter instance the differential diagnosis must sometimes depend to a certain extent upon the presence of tender nodules in the intercostal spaces and the fact that pressure upon them will cause an immediate reference of pain to the abdomen or an attack of pain.

In generalized intramuscular fibrositis, often referred to as common muscular rheumatism, the symptoms are usually an aching stiffness in one or many regions, and soreness or tenderness which are often characterized by migration and frequency of remission. The pain is altered by seasonal and climatic conditions. Fatigue is often a marked symptom. Often the pain and stiffness are worse on arising or after a period of rest or inactivity. Tender spots and nodes the size of a grain of wheat or larger, associated with subcutaneous thickenings may be palpated particularly along the origin of muscles in the lumbosacral, gluteal, or the cervical, upper thoracic or trapezius regions. These nodes and fibrous thickenings are considered the sign posts of the disease. English writers particularly stress the diagnostic importance and apparent ease of finding nodules. Some insist on their presence for a diagnosis; others admit that in many cases of fibrositis no nodules are felt.

In the periarticular type of fibrositis the pathological process affects chiefly the fibrous capsule and the surrounding ligaments. The synovial membrane, which after all is the inner lining of the capsule, may be affected to a more or less extent but pannus formation and invasion of cartilage and articular bone do not usually occur. It is likely that fibrositis is present to a certain extent in every case of chronic rheumatoid arthritis but, fortunately, every fibrositis does not have an associated or eventual arthritis.



The symptoms and physical findings of periarticular fibrositis are well illustrated by this thirty-eight-year-old male who comes to the clinic complaining of pain in the left knee and in the left hip of two years' duration. He was born in Scotland, and has had good health all his life except for the present illness. The pain was first noticed in the left knee and about a week later in the left hip. The pain is a dull ache, is not present during ordinary degrees of motion or when he is at rest. Overuse of the joint or any untoward movement causes pain. There is a good deal of stiffness associated but there has been very little limitation of motion. There has been no swelling or redness of the joints. He tires easily and feels exhausted toward the end of the day. During the past two years he has had two or three periods varying from a week to three weeks during which time he has had very little discomfort. He was told by a physician that he had rheumatism and received several injections of vaccine but with no benefit.

The essential physical findings are: the sinuses are clear, the teeth are removed, the tonsils are enlarged and cryptic; pus can be expressed from the left, the pharynx is injected. The lungs, heart and abdomen are normal. The prostate is smooth, firm, not enlarged and not tender. The reflexes are normal. The left knee is not swollen, there is no redness or crepitus. Just above the left patella there is marked tenderness and a small firm tender nodule the size of a pea, and 2 smaller ones about the size of grains of wheat can be palpated. These nodules are exquisitely tender. There is slight tenderness over the medial surface of the left knee. Extreme flexion and extension of the knee causes pain. There is no redness or swelling about the left hip. There is free motion at the hip but abduction and flexion of the thigh causes pain just below the iliac crest. Pressure in this area reveals tender spots but no nodules are felt. There is tenderness just lateral to the sacro-iliac joint. x-Rays of the left knee and of the pelvis are normal. The Wassermann and Kahn tests are negative, urine normal, prostatic fluid clear. The leukocyte count is 9200, red blood cell count 4,820,000, hemoglobin 86. Cultures from

the nose showed *Staphylococcus albus* and from the throat *Streptococcus viridans*.

From the symptoms, physical findings, course of the disease and laboratory and x-ray findings, it is likely that this patient has a periarticular fibrositis involving the left knee and left hip.

In the early days or weeks of a periarticular fibrositis it may be difficult if not impossible to be certain that a true rheumatoid arthritis is not impending. In periarticular fibrositis manifestations of systemic change are few or absent; loss of appetite and weight, anemia, and general debility are seen to a much less extent than in arthritis. The joints themselves are less tender in fibrositis than in rheumatoid arthritis, and in fibrositis the swellings are absent or slight and x-rays show no articular disorganization over a period of time.

There are no laboratory data distinctive of fibrositis.

**Treatment.**—The treatment of fibrositis depends to a large extent upon the cause, and in every case the effort should be made to arrive at an etiological diagnosis, as only then is proper treatment possible. The three most effective therapeutic measures are: (1) elimination of foci of infection, (2) rest, (3) physiotherapy. Foci of infection are usually apical dental infections, pyorrhea alveolaris, infected tonsils, infected nasal sinuses, pyosalpinx, cervicitis, prostatitis, septic seminal vesicles and occasionally cholecystitis or bowel infections. Careful search for these foci of infection should be made and proper treatment given.

Rest is one of the most valuable therapeutic agents, and should be prolonged as long as conditions warrant. Fixation by strapping should be done wherever possible. The reduction of occupational or other trauma is important. Heat is usually effective in relieving the symptoms, and is perhaps best supplied by an infra-red lamp or an ordinary electric heater for an hour two or three times a day. After the use of the heat lamp gentle massage with equal parts of oil of wintergreen and olive oil or some mild counterirritant is of value. Hot baths are useful. The salicylates are usually effectual in alleviating the acute symptoms, perhaps best given as sodium salicylate to-

gether with calcium gluconate a gram of each four times a day. If the pain is severe and agonizing, the opiates may have to be resorted to temporarily. The bowels should be freely opened, and large amounts of water and fruit juices taken. In the chronic conditions building up the general health by an adequate diet, fresh air and sunshine is often effective. Persons subject to the condition should be warmly clothed, and avoid if possible, exposure to cold and damp.

English workers report good results in the treatment of fibrositis in the subacute and chronic stages by forcibly breaking down the fibrositic cords and nodules by manipulation. The object of the manipulation treatment is to burst the nodule by a sudden and forceful pressure of the finger tips which is calculated to tear asunder the agglutinated fibers. This can be done by combining a rapid to and fro movement with the pressure. This treatment can only be adapted where the cord or nodule can be compressed against subjacent bone, and also where no structure occurs such as nerves and tendon sheaths that might be damaged by the force used.

The use of vaccines in the treatment of fibrositis is usually unsuccessful, although English workers report good results by injecting a lipovaccine (polyvalent streptococci isolated from rheumatic patients and suspended in sterile olive oil) into the inflamed tissue. Fever therapy may help in some cases but too much cannot be expected from its use.

### MYOSITIS

Myositis is an inflammation of the muscles; the voluntary muscles are alone affected in all the varieties except the two known as dermatomyositis and polymyositis haemorrhagica when the heart muscle is also implicated. Myositis has long been known as a primary or secondary disease. The myositides which occur in septicemia, ulcerative endocarditis, trichiniasis, actinomycosis, gonorrhea, pneumonia, typhoid and syphilis are plainly of secondary origin. Primary myositis occurs as an acute, subacute or chronic affection and is seen in two chief forms—the suppurative and the nonsuppurative.

**Primary suppurative myositis** is sometimes single but generally a multiple muscle inflammation, mostly acute, of bacterial origin, presenting the picture of an infectious disease and generally ends in suppuration. Various organisms of the pus-producing type have been isolated but most workers find *Staphylococcus aureus* in every instance. Small infected wounds, furuncles, acne pustules, etc., may serve as the original portal of entry, and apparently the mucous membrane may also at times act in this capacity. Muscles may be made susceptible of invasion by trauma, overexertion, or hyperemia.

Three principal varieties of primary suppurative myositis are recognized: (1) large solitary abscesses in muscles, (2) disseminated abscesses in muscles, and (3) diffuse purulent infiltration of the muscles. Most of the cases belong to the first group.

This young married woman, age twenty-two, the mother of one child, was entirely well until one month ago. At the time she retired feeling quite well and awoke after a short nap with a feeling that her legs had gone to sleep. She got out of bed without difficulty but while doing so noticed transient sharp pains in both knees. After walking about a little the posterior group of muscles of both the thighs seemed to go into spasm, and became quite sore. She went to bed again but when she awoke she found that both upper legs were quite painful, and she could not bend her knees. Her throat was quite sore and she had a temperature of 102° F. A physician made a diagnosis of rheumatism and prescribed treatment. After remaining in bed at home for ten days with no improvement, she was sent to the hospital. Efforts while there to remove pus by needle were unsuccessful. She remained in the hospital ten days and had a temperature of 100° to 103° F. every day. She showed some improvement and was sent home. However, the condition did not subside and she came to the clinic.

The past history, family history, inquiry by systems are essentially negative to the present illness.

The physical examination was essentially negative except that there was marked tenderness, indurative swelling and

hyperthermia over the posterior group of muscles of the left thigh. The muscles of the right thigh were tender and slightly swollen but to a lesser extent than the left.

The leukocyte count was 17,500, hemoglobin 70, red blood cell count 3,800,000. The urine is negative. Wassermann and Kahn tests are negative. Cultures from the throat showed *Streptococcus viridans*; those from the nose *Staphylococcus albus*. x-Rays of the thighs showed no bone or periosteal involvement. Aspiration about the middle of the posterior surface of the left thigh with a large needle produced about 50 cc. of thick yellow pus. Two large incisions were then made and 400 cc. of pus were obtained. Cultures of the pus showed a heavy growth of *Staphylococcus aureus*. No anaerobes were found.

The source of this infection is not definitely determined; its origin is most likely through the mucous membrane of the nose and throat.

**Dermatomyositis** is an acute or subacute inflammation of the muscles of unknown etiology associated with edema and dermatitis. It is characterized by a gradual onset with pain, rigidity and tenderness of the muscles, edema of the extremities, and a rash resembling one or another of the exudative erythemas. In addition there are general symptoms of malaise, anorexia, general debility and fever. As a general rule the inflammatory condition is not confined to the muscles, though acute pain and stiffness of the muscles with prostration, constitute a big part of the picture; inflammation in the skin, mucous membranes, nerves, spinal cord or serous membranes may be associated with the myositis to varying degrees. The skin over the affected muscles is edematous and the dermatitis takes various forms—erythematous, urticarial or erysipeloid. The skin lesions most often resemble erysipelas but differ from the latter in that reddening, though varying in degree, may last for weeks in the same place. When the mucous membranes are involved severe vomiting or diarrhea or both may occur, ceasing, however, long before the myositis does if the condition does not end fatally. When the serous membranes are involved peritonitis, pericarditis or pleurisy may occur.

The muscles become too painful to be used; the course is usually progressive, and after some weeks or months death may result from involvement of the muscles of deglutition or respiration, perhaps with bronchopneumonia. If the patient survives there are generally deformities from fibrotic fixation of the substance of the muscles leading to various contractures and deformities but these differ from the effects of rheumatic arthritis in that they are not especially related to the joints.

The disease must be distinguished from trichiniasis but in this disease the symptoms are first those of a pyrexial gastro-enteritis, these being followed by acute pains and aches all over the body, particularly the muscles. The muscles swell, the face and neck and trunk are affected as well as the limbs, the face and eyes become edematous, high fever is not rare and eosinophilia and leukocytosis are usual. Adult trichinella may be found in the stools and larval trichinella in portions of the affected muscle; encysted larvae may be found in the affected meat that gave rise to the attack should any of it have been preserved.

*Polymyositis haemorrhagica* is an acute, subacute or chronic disease, of unknown etiology, strongly resembling dermatomyositis but differing from it chiefly in the presence of interstitial hemorrhage between the muscles and occasionally by circulatory symptoms caused by impairment of the cardiac muscle. Purpura and hemorrhages from the mucous membranes may occur.

*Myositis ossificans* is the abnormal growth of bone in muscle or fascial planes. It occurs in two chief forms—localized myositis ossificans and progressive myositis ossificans. Local myositis ossificans may occur after repeated injuries or a single severe one.

This patient, aged sixteen, while playing football about three months ago was tackled hard, receiving the blow on the lateral side of the right thigh. The right thigh muscles became swollen and tender, and the patient could not bend the knee. The skin was not broken and no blue areas were noted. About a week later he noted a hard, firm mass on the anterolateral aspect

of the right thigh. The stiffness and tenderness persisted, and he came to the clinic.

Examination at that time revealed a diffuse, hard, firm mass on the lateral aspect of the right thigh. It was about 25 cm. long and about 3 cm. wide, and extended from just below the lesser trochanter to the junction of the middle and distal third of the thigh. x-Rays showed the bone mass as described. The CO<sub>2</sub> combining power was 65.3, serum pH 7.57, serum calcium 10.7 mg. The leg was put in a long leg cast which was bivalved, diathermy was given three times a week, a low calcium diet and large doses of ammonium chloride were prescribed. At the present time, two months from the first visit, the tenderness and pain have disappeared, the knee can be completely flexed, and the bony mass has decreased to about one third its former size.

**Localized myositis ossificans** is occasionally seen in the adductor longus (rider's bone) following bruising or partial rupture of the muscles, occurring especially in cavalry soldiers, and in the deltoid and pectoral muscles of soldiers (drill bone) from bruising by the rifle in drill. The diagnosis has to be made from hematoma, new growths and exostoses. The history and x-ray study are important in differentiating these conditions. Local myositis ossificans reaches its maximum size rapidly, and usually diminishes slowly.

The **progressive form of myositis ossificans** is an irregular, generalized, progressive ossification in or adjacent to the voluntary muscles. Because of the hardening process in the neighborhood of the joints ankylosis usually supervenes. The cause of the disease is unknown. The antecedent factors are usually injury, excessive muscular strain or chronic disease of the joints. Microdactylia or valgus deformity of the great toe and thumb occur in 75 per cent of the cases. The process usually begins in the neck or back with swelling of the affected muscles, redness of the skin and slight fever. The later subsidence of the process is not complete, induration persists, followed by fibrosis, and this then becomes the seat of bony deposits, growing progressively harder as the process

continues. The disease involves chiefly the muscles of the trunk, upper extremities and neck, trapezius, latissimus dorsi, sternocleidomastoids and shoulder muscles. Death usually results within a few years from intercurrent disease such as bronchopneumonia or from involvement of the masseter muscles and starvation.

**Treatment.**—The treatment of primary suppurative myositis is mainly surgical, and depends for its success on early recognition. Before localization occurs hot boric acid application may hasten the process. The treatment of dermatomyositis and polymyositis haemorrhagica is very unsatisfactory. Until some further progress is made in the knowledge of the infection and immunity to the disease, one cannot reasonably expect specific therapy. Rest in bed, baths, fomentations and massage will ameliorate the symptoms, and probably modify the stiffness and tenderness which are so annoying. Various analgesics have been tried, including the salicylates, but no particular drug has been found to offer any special advantage. It is important to keep up the patient's nutrition by an adequate diet. Fortunately these conditions are rare.

The most important therapeutic measures in local myositis ossificans are: (1) rest, (2) immobilization when possible, (3) diathermy, (4) elimination of foci of infection, (5) a low calcium diet, (6) relatively large doses of ammonium chloride may be tried. Surgical excision may be indicated in some cases. The medical treatment of the progressive form of myositis ossificans avails very little. The removal of the bony masses has been done with unsatisfactory results as there is usually a recurrence at the site of removal in almost every instance. By exercising precautions against trauma, and by the use of the therapeutic measures indicated in the localized form of the disease, the affection can occasionally be prevented or at least delayed from spreading.



## CLINIC OF DR. THOMAS L. FENTRESS

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### RECOGNITION AND MANAGEMENT OF DEFENSIVE AND WORRY NEUROSES

**Case I.**—The first patient I wish to present today is M. M., a white married woman of fifty-five. She complains of numbness of the hands, occipital headache, insomnia, urinary frequency, and constant burning and itching of the vulva and anus. She states that she has been "nervous" for thirty-one years and that during the past three years her present symptoms have become progressively worse. The past surgical history is of interest. She was married at the age of twenty. Three years later she had an operation on the cervix uteri and after another five years she had a suspension of a retroverted uterus. Twelve years after her marriage the right ovary was removed because of a dermoid cyst. The following year this patient had an appendectomy for chronic appendicitis. Two years later she had a tonsillectomy and in the same year a supravaginal hysterectomy. Recently a proctologist reported perianal kraurotic changes as the cause of her pruritus and advised surgery, but the patient refused to submit to this operation. The general medical examination was within normal limits. The neurological examination was negative and no objective sensory disturbances were demonstrable.

The patient was born in Sicily and is the oldest child in a family of six. The father was a railroad laborer who was rarely at home. He died at sixty of a urinary tract infection. The mother is alive at seventy-six, and has long been an invalid

because of "neuritis." As a little girl the patient was a "tomboy," physically a match for her younger brothers. During her father's long absences she was always eager to help her mother with the heavy work, but had no interest in sewing and cooking. When the patient was nine the father went to the United States, and two years later she came here with her mother and the younger children.

The first menstrual period occurred when the patient was fourteen. She was very alarmed and feared that she had injured herself in some of her tomboy activities. She could not bring herself to tell her mother, and when the truth was discovered the mother gave her a minimum of information and did not reassure her. From that time on the patient states that she had severe cramps during each period which forced her to go to bed. The patient subsequently gave up all "tomboy" activities and spent her time helping her mother do piece work sewing at home. She had little in the way of social life and out of deference to her mother's wishes married an Italian five years her senior when she was twenty years old. Her sex life began with dyspareunia and vaginismus and continued with complete anesthesia. She has never been pregnant.

At the time of her marriage the patient's husband was employed in a restaurant. Within a few years he became the proprietor and the business prospered. During these years the patient remained at home a nervous housewife, with no social interests or outside activity, except as a patient in various surgical wards. After forty years in this country her English is still very poor. During the late 1920's the husband's business expanded, and in 1933 he lost everything. He reacted to this failure with a depression and for two years was on relief. At present he has a position as a private policeman, but apparently has not the courage to make a "come back."

Since the husband's failure the patient's condition has become much worse. She showed no inclination to find employment outside her home or to aid her husband in any practical way.

The psychological treatment in this case was begun with a

study of the patient's dreams, several of which were sufficiently clear to be worth repeating. The first dream consisted of a group of women, including the patient, admiring a young woman who was nude to the waist and had no breasts. Another dream was of the patient trying to drive a small automobile up a mountain road. The mother who was beside her became so anxious that it was necessary to abandon the attempt and back the car down the hill. These dreams contain the two main features of her neurotic conflict—the admiration of the masculine woman and the fact that she had been forced to renounce this ambition.

The patient has been able to accept these facts, but has not the courage to attempt a more masculine adjustment at the age of fifty-five. In the light of her present inability to adopt a more aggressive rôle the exacerbation of her symptoms at the time of her husband's failure becomes understandable, as this presented a challenge to this dormant side of her personality. The pruritus and the paresthesias of the hands are probably related to an early masturbatory conflict, but as is frequently the case in older women, this view could not be confirmed. From a therapeutic standpoint, little is to be expected beyond some amelioration of her more distressing symptoms.

The chief interest in this case is the surgical history. She is a type of woman who is unable to accept the feminine rôle without conflict. She had dysmenorrhea and dyspareunia, and never became pregnant. Anatomically she had a retroverted uterus and later developed an ovarian dermoid. Without presuming to express an opinion as to whether the physiological and anatomical findings are the cause or the effect of the psychological syndrome, it is of interest how frequently this psychophysical parallel is encountered. From the surgeon's viewpoint it is well to remember that a patient who seems to require a series of operations on the pelvic viscera, or any other organs for that matter, may be expressing an unconscious need to injure the organs in question. In the case of this patient if a plastic could have changed her sex, no doubt a single operation would have been successful.

**Case II.**—Our second patient today is R. A., a white male of twenty-nine, who complains of attacks of palpitation, vertigo, sweating, trembling, during which he feels like a cornered rat. The patient must escape at any cost. The past medical history reveals bronchial asthma as a child and lobar pneumonia in adult life. Neurological examination is entirely normal. There is a static tremor of the extended hands which are cold and sweating and a pronounced sinus arrhythmia.

The patient is an only child. His father is sixty-two, and a successful physician. His mother is fifty and in good health. Apparently their marriage has been unhappy. The mother is a domineering type who is athletic, a bridge expert, and a leader in women's organizations. There is something masculine about her appearance, and she wears the pince-nez glasses of a successful woman executive. She has never been able to adjust to the sexual side of marriage and has been unwilling to bear another child.

When the patient was a small boy he had severe bronchial asthma. During the northern winters, his mother would take him South for several months, leaving his father in Illinois. Each year these winter vacations became longer until finally the father moved to Florida where the family made a permanent residence.

Throughout his childhood the patient shared a bedroom with his mother and the father had separate quarters. The father was completely engrossed in the practice of medicine and his relaxation at home was usually *solitaire*. The mother always nagged him about the way he snapped the cards as he laid them out and criticized his table manners and dress. Apparently he was oblivious to her remarks.

The patient was treated very indulgently by the mother. However, she insisted on his maintaining a creditable standing at school. He always found his studies easy but was usually so apprehensive in examinations that he never did himself justice. Finally at college during an examination he became so tense that there was a spontaneous orgasm. After this, his examination fears became so severe that he failed in his first

year at medical school. This failure filled him with remorse. He deliberately exposed himself to the cold weather insufficiently clad and subsequently developed a lobar pneumonia during which he wished to die. After his recovery he returned to the family home and made no further attempt to continue his medical education or find other employment.

The sexual education of the patient was another point at which he was confronted by maternal discipline. Although he shared a bedroom with his mother until he went to college he was supposed to possess no sex information. During his teens he was frequently accused by her of masturbation and his sheets were always examined for any evidence of nocturnal emissions. The patient denies any overt sexual behavior until his senior year at college when he had an affair with a girl who was his social inferior. This was terminated by the mother who paid the bill for an abortion.

About one year ago the patient became infatuated with another woman ten years his senior whom he realized he could never marry because of the difference in their religions. He states that their sexual relations, although frequently perverse in character, were mutually satisfactory. However, he frequently experienced an overpowering desire to escape from her. When his mother realized the depth of this attachment she advised him to give up this woman and to frequent prostitutes. She made the definite statement that he could never marry because it was his duty to live with her after the death of his father. When the patient could not be persuaded to terminate the affair, he was referred to a local psychiatrist who advised sending him away.

The mother found the patient a position in Chicago as a salesman and arranged with his employer that he be paid a salary whether he was able to sell or not. A maternal aunt provided a home for him. Psychological treatment was undertaken at this time.

The patient proved to be very cooperative and intelligent. After several weeks of psychotherapy he began to develop an interest in his emotional dependence on his mother and also

his antagonism to her. He also came to the realization that the second woman was a mother substitute. His panic attacks disappeared, and he surprised his family by actually making a success of selling. He made various social contacts and new friends.

At this point the mother came here from Florida. As soon as she sensed that the patient's attitude of dependence was being broken she insisted that her son discontinue the treatment and return to his home. As might be expected he has agreed to comply with her wishes.

This case has been presented to illustrate the importance of the home environment in the etiology and continuance of a psychoneurosis. It has not been attempted to deny that there was probably some constitutional factor which made this patient likely to develop a psychoneurotic reaction. However, the history plainly demonstrates that the mother's inability to solve her marital and maternal relationships was an important factor in the patient's emotional attitudes. When one speaks of hereditary factors in psychoneurotics, it is frequently a situation of this kind which is meant. In this sense the "sins of the fathers may be visited upon the children even unto the third and fourth generations."

**Case III.**—The next patient I wish to present is L. N., a white married woman of forty-two. She complains of pains in her lumbar spine radiating up to the neck, occiput and both her eyes. The pain began six months ago when she had a pyelitis after a miscarriage. She had the ureter dilated and was told she had a fallen kidney. When the pain persisted a tonsillectomy was performed. Osteopathic treatments for a "displaced vertebra" were without benefit. Thorough examination by an eminent internist revealed minimal osteo-arthritis of the spine, slight obesity, and two infected teeth. Neurological examination is within normal limits. The past medical history is unimportant.

The patient's father is a retired clergyman of seventy-five who has a carcinoma of the stomach. Her mother died of

myocarditis at fifty-seven. The patient has two older sisters, one married, and one a school teacher. A brother died at twenty of pulmonary tuberculosis. There is no family history of nervous or mental disease. Ten years ago the father married a widow of fifty. This was against the wishes of the patient who is still unreconciled to her stepmother.

The patient states that as a child she resented the fact that the father's income was inadequate and the mother was always overworked. She had many plans to improve the situation. She did well in school, took a business course, and got a good position at eighteen. She continued to live at home and gave her salary to her mother. She married at twenty-four, rather impulsively, a soldier who was preparing to leave for France. After two weeks of married life he sailed and was subsequently killed in action. The patient was not particularly disturbed by this. She states that the sexual side of marriage meant nothing to her, although she wanted to have a child.

After the death of her husband she continued to hold a good position and to live at home. She became interested in various charities and finally started to give night courses in English to immigrants. One of her pupils was an intelligent Swedish inventor who was utterly impractical and unable to earn a comfortable living. Nine years ago she married this man but insisted that her unmarried sister share their home. (This marriage was probably related to the second marriage of her father a year before, which was previously mentioned.)

After the second marriage the patient made a fair adjustment as a housewife. She and her sister invested their savings in the husband's inventions which always turned out to be disappointing. The only difficulty in this household was constant friction between the sister and the husband, especially over money matters. About a year ago the patient became pregnant for the first time. The husband was enthusiastic about the prospect of a child, but the sister was most unkind stating that the patient was too old for child-bearing. At about five months the patient had a miscarriage without apparent cause. This was followed by a pyelitis and pain in the back. About this

time the patient developed a compulsive desire to lift a heavy buffet in her dining room. This would aggravate her backache. In spite of the pain she would experience an overpowering temptation to lift the buffet and would finally yield until this became a daily ritual.

The treatment of this patient from the psychologic side began with a study of her compulsive lifting. It was obvious that she was deliberately attempting to aggravate her backache and her nervous condition. Her purpose in doing this was to worry her husband. She soon began to express her hostility to him quite openly, keeping him awake most of the night with interminable discussions about lifting the furniture, vomiting if he was late to dinner, threatening to make home so unpleasant that he would have to leave her, and harping on his economic inadequacy. Conscious death wishes against him were also present. The patient reacted to these with remorse and began to make threats of suicide which, however, were never attempted. She was mildly depressed at this time. Finally she began to understand that her hostility to her husband was merely another instance of her lifelong reluctance to make a feminine adjustment. Her compulsive lifting disappeared and she insisted that her sister move away. She is now attempting to develop a more normal attitude to her marriage with its economic insecurity and childlessness. Her backache is still present but is less severe and recently she has been benefited by massage and physiotherapy.

This case has been presented to demonstrate the inadequacy of the physical viewpoint in treating a backache. We have a history of an acute infection before the onset of the pain, x-ray evidence of osteo-arthritis of the spine, and a chronic dental infection. However the most important feature in this case was a compulsion to lift heavy furniture with the intention of aggravating the pain. When the motives behind this apparently irrational behavior were understood it became possible for this patient to attempt to work out a better solution of her emotional difficulties. As this adjustment becomes more successful the psychological need for her pain will continue to diminish.



Before concluding this clinic a few general remarks about psychoneurotic reactions might not be amiss. The various contemporary schools of psychiatric thought may disagree on therapy or on the importance of heredity, infection or other physical factors in the etiology of the psychoneuroses, but the opinion is becoming increasingly accepted that a psychoneurosis can be understood only psychologically. Consequently the time-honored method of diagnosing a psychoneurosis by excluding organic disease is no longer valid. A patient with panic attacks like the second case presented today has a characteristic history which is just as typical as the history of duodenal ulcer and with which all physicians should be familiar. The rational treatment of the psychoneurosis is some type of psychotherapy and should be instituted promptly, not years after ill-advised and unsuccessful surgery, as in the first case presented today. There is no reason why the general practitioner should be unable to undertake minor psychotherapy with the same confidence with which he does minor surgery. Success in either requires only a frank realization of his limitations as a therapist and a willingness to ask for assistance in his more difficult cases.



## CLINIC OF DR. EDWARD J. STIEGLITZ

### THE CHICAGO MEMORIAL HOSPITAL

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#### CLINICAL APPLICATION OF RENAL FUNCTION TESTS

DIAGNOSIS by merely giving a disease a name does not suffice. There are many forms of Bright's disease, differing widely in etiology, symptoms, progressiveness, prognosis and in the character and extent of depression of functions. Comprehensive diagnosis should include consideration of the probable *etiology*, the *pathologic lesions* and the type and degree of *functional impairment*. In renal disease, etiology and the functional status of the kidneys are the more important considerations. Curative therapy frequently depends upon recognition and correction of etiologic factors. It is wholly impossible to judge the severity of renal injury on either the intensity or duration of such common symptoms as albuminuria, edema, casts, and arterial hypertension alone. Many of these phenomena may be due largely to extrarenal factors; this is certainly true of edema and/or hypertension. Diagnosis, especially in chronic disorders, should include quantitative impressions as well as qualitative.

Functional studies are, therefore, necessary for proper diagnosis in renal disease. It is characteristic of all normal living structures to have a wide margin of safety or functional reserve. The existence of such reserve is most conspicuously manifest clinically in the heart, for we can readily observe the phenomena of increased cardiac effort when the circulation is placed in a state of stress. *Symptoms* of failure do not appear unless the functional demand is actually greater than the functional capacity. Thus, for example, in heart disease, functional evaluation depends not upon the phenomenon of dyspnea, but

upon the *degree of effort* necessary to induce dyspnea. In frank cardiac decompensation dyspnea appears without added effort; the labor of mere existence is greater than the functional capacity. A similar, but less readily dramatized, situation exists in the problem of renal functional capacity. There are no pathognomonic symptomatic evidences of renal functional impairment *until* the functional burden exceeds the functional capacity, or, in other words, until the functional *reserve* has been depleted to the point of renal decompensation. At such a point, resulting in the state commonly called "uremia," functional studies become largely unnecessary; the functional failure is then conspicuous. But before this occurs there is usually a long period of *impaired reserve*, the detection of which depends upon renal function studies. We start life with a renal margin of safety of about 400 per cent; the normal young animal can maintain health with one-half of one normal kidney. Inevitably, through transient infections and the multitude of insults from the vicissitudes of existence, this margin is gradually depleted. Such depletion is, of course, tremendously accelerated by actual renal disease; acute nephritis may quickly reduce the functional reserve to below normal requirements, although renal decompensation or uremia occurs more commonly after years of chronic nephritis.

The objectives of renal function study in clinical practice are both qualitative and quantitative. Such study may be applied to determine whether or not functional injury exists. as, for example, in orthostatic albuminuria, where, despite the profuse proteinuria, the renal functions are essentially normal. Following a febrile albuminuria it is wise to determine the renal functional reserve by appropriate tests to insure against diagnostic error and avoid missing a latent nephritis. In acute nephritis function studies are especially indicated after the subsidence of acute phenomena; it is necessary to have a base line for future comparison in order to measure progress—progress in either direction. In such instances, as in chronic nephritis, it is best to repeat such studies at intervals.

In hypertensive arterial disease<sup>1</sup> renal function studies are

of the greatest importance. Etiologic correlation between nephritis and hypertensive disease may occur in three ways: (1) renal impairment may cause hypertension; (2) hypertensive disease may impair the renal function through malcirculation (nephrosclerosis), and (3) both the arterioles and renal parenchyma may be injured simultaneously. Where hypertension is not due to nephritis, and this group includes the great majority of cases of hypertension,<sup>2</sup> repeated determination of the renal functional reserve makes possible observation of the progressiveness of nephrosclerotic changes.

Another field of usefulness for clinical renal function tests is in genito-urinary diseases where the problem of renal efficiency is often of paramount moment. Lastly, but by no means of least significance, renal function studies are often urgently indicated in the care of pregnant women. Prenatal application of such studies serves to detect latent or "silent" renal damage from early infections and/or previous pregnancies and thus forewarn of difficulties. In the "toxemias of pregnancy" renal function tests will frequently distinguish between preexistent nephritis and late renal fatigue. As the prognosis and therapeutic management of the various types of nephritis in pregnancy differ widely, it is of great importance accurately to differentiate the types.<sup>3</sup> Too many instances of preexistent nephritis go undetected in obstetric practice and, as a result, the exacerbations induced by pregnancy do extensive, irreparable harm. Whenever there is reason to suspect the possibility of previous renal injury from the history of the patient, preconceptional study of the renal functions is indicated. It has come to pass that young women with known heart disease frequently consult a physician for advice and prognostic information before marrying or before risking pregnancy. It is unfortunate that the opportunity for similar preconceptional evaluation of the renal reserve is not more frequent. The fact that the burden of renal reserve is inevitably and considerably increased during many weeks in pregnancy must not be forgotten; the functional *reserve* thus assumes particular significance prior to such predictable stress.

## PHYSIOLOGIC ASPECTS OF THE RENAL FUNCTION TESTS

The functions of the kidneys may be conveniently divided into four major activities: (1) elimination of waste water (solvent); (2) elimination of waste (metabolic) solutes, which include both electrolytic salts and the organic *débris* of metabolism; (3) elimination of substances foreign to the body and especially those foreign to the blood stream (such foreign substances may or may not be noxious), and (4) aid in maintaining the acid-base equilibrium of the body.

Certain of these functional activities are open to clinical investigation. One may measure the renal response to a demand to secrete water quickly (the solvent), the ability of the kidneys to concentrate the urine (secretion of solutes), the effectiveness with which certain substances, such as urea, are cleared from the blood stream, and, with appropriate materials, study the excretion of foreign substances. Failure of the kidneys to maintain a normal acid-base balance is detectable, but, as yet, we have no satisfactory clinical test for measuring the *reserve* power of the kidney to cope with such disturbed equilibrium.

Physiologic evidence indicates that the greatest part of the renal work is expended in concentrating the urine. It is probably more work for the kidneys to excrete a small volume of highly concentrated urine than a large volume of dilute urine. As all procedures intended to determine *reserve* depend on the response to increased effort, this fact becomes of great significance in evaluating the various function tests. To detect hidden weakness or weakened reserve, it is necessary to create conditions of stress, for under the normal load the structure may be perfectly competent. The tests involving stress are thus the most sensitive to early or minor damage. This is true both theoretically and in actual clinical application, although the "stress tests" are not necessarily also the most satisfactory for accurately determining variations in the renal functional capacity when *extensive* injury exists.

Almost innumerable test procedures have been suggested at one time or another. Many of these have been found want-

ing. We shall limit ourselves to three or four procedures of proved merit, each with relatively specific indications, and discuss their significance and limitations. The essential criteria of a practical clinical function test are: (1) physiologic soundness; (2) specificity for the functions or structures studied; (3) safety; (4) simplicity; (5) relatively uniform normal response, and (6) sensitivity sufficient to reveal impairment not too far removed from the borderline of normal. Because elaborate laboratory facilities are not always available, simplicity is necessary if the procedure is to serve the largest number of patients possible.

### TESTS

Concentration of the urine requires a major fraction of renal effort. The response of the kidneys in concentrating the urine under conditions of stress is unquestionably the most sensitive test for early depletion of reserve function. To force the kidneys to secrete a highly concentrated urine, if possible, is the equivalent of asking the renal parenchyma "to climb a hill" and thus weaknesses are brought to light. Such stress conditions obviously can be induced in either one of two ways: (1) by the addition of solute, and (2) by the withdrawal of solvent (urates).

The first of these methods is illustrated by the **urea concentration test**, introduced by Maclean and de Wesselow.<sup>4</sup> The procedure is as follows:

After eighteen to twenty-four hours with a small intake of fluid and at least three hours after food, the patient voids and immediately thereafter takes by mouth 15 Gm urea dissolved in 100 cc. of water. Urine specimens are obtained *one and two hours* after the administration of the urea. These are examined quantitatively for their urea content. During this two-hour interval the patient takes no food or drink.

If *either* specimen contains urea in excess of 2 per cent the renal function is considered normal. The higher the *concentration*, the greater is the renal functional reserve. Diuresis, of course, will cause dilution and, therefore, the test is deemed satisfactory only if not more than 120 cc. urine are secreted in

the second hour. Urea itself may cause considerable diuresis in the first hourly interval. This test has proved to be very valuable, is sensitive, safe and involves only two urea determinations on the urine. It is definitely a "stress test" and reveals early impairment.

Similar conditions of stress may be induced without the introduction of anything into the patient, by depriving the body of water for a stated period. This concept has been the basis for many test routines which differ slightly in detail but have the same basic principles. Perhaps the simplest and most satisfactory routine is that of Fishberg.<sup>5</sup> The technic for his **renal concentration test**, as carried out in this clinic, is:

The patient receives no fluids or food after the usual supper until the test is completed. At 7 A. M. the patient voids and this specimen is discarded (this urine was secreted during the night). At 8 A. M., 9 A. M., and 10 A. M., respectively, separate specimens of urine are collected and marked with the hour of voiding. The object of the test is to obtain specimens of urine as concentrated as possible after the body has been deprived of water for fourteen to sixteen hours. It is not essential that the urine be voided exactly on the hour as long as the collections fall within the period of 8 to 11 A. M.

The specific gravity of these specimens is then determined, and the highest specific gravity taken as a measure of the concentrating capacity of the kidneys. Normally, at least one specimen reveals a specific gravity of 1.025 or higher; the normal range is from 1.026 to 1.034 under these standardized conditions of relative dehydration. Failure of the kidneys to concentrate the urine above a specific gravity of 1.020 is indication of definite impairment of functional reserve. The lower the maximum specific gravity, the poorer is the renal functional capacity. In renal decompensation the maximum concentration is often about 1.010.

There are several sources of error which deserve mention. Most important and frequent of these is the error introduced when diuresis occurs from water stored in the tissues; the test is valueless and misleading if carried out during the subsidence of edema. With edematous patients, therefore, great caution must be observed in interpreting results which show low urinary



concentration. The occurrence of edema loss can be confirmed by observation of changes in body weight and/or by repetition of the test under better conditions. Accurate measurement of the specific gravity with calibrated equipment is essential. An obvious, but often ignored, error is introduced by failure to have the urine at 21° C. when the specific gravity is measured; almost all hydrometers are calibrated at this temperature. Determinations made on freshly voided (warm) urine and/or urine from the refrigerator are absolutely worthless. Very large amounts of protein in the urine raise the observed specific gravity and thus mislead, for the protein is not a true secretory solute. The specific gravity is increased 0.003 by 1 per cent dissolved protein or 1000 mg. albumin per 100 cc. of urine.<sup>6</sup> Such severe albuminuria is observed but very exceptionally. Small amounts of protein do not affect the results appreciably.

This is the simplest of the renal function tests. It is readily carried out with a minimum of equipment, requiring chiefly only intelligent observation and interpretation. It can be a routine office procedure with proper instruction of patients; I believe it should become one. It is obviously wholly devoid of risk to the patient. But it is commendable primarily because: (1) it is thoroughly physiologic in principle, and (2) it is *the most sensitive test in detecting minor degrees of reduction of the renal function*.<sup>1, 3, 7, 8</sup>

Of the many other related procedures, that suggested by Mosenthal<sup>9</sup> is the best known and most useful. By administering known volumes of fluid at specific hours and obtaining urine at intervals of two hours during the day, it is possible to gauge not only the ability of the kidneys to concentrate the urine, but also the promptness with which ingested water is eliminated. This **concentration-dilution test**, however, yields but little more useful information than the simpler procedure just discussed.

The advent of accurate methods for the quantitative chemical analysis of blood produced a towering wave of enthusiasm for "blood chemistry" as a means of diagnosis. More recent microscopic methods, which require but a few drops of blood,

have further accelerated clinical studies. We are deeply indebted to the chemist for these methods, but we must not be misled by blind faith in laboratory data just because they are derived by methods of precision. No matter how accurate the analytical method, the significance of the data depends upon our understanding of the *physiologic* variables. In human biology these are legion. I do not want to belittle the value of blood chemical analysis; in many instances such studies reveal the basic disturbances responsible for obscure phenomena. The hypoproteinuria of nephrotic edema, discovered by such clinical studies of the blood, is an example. In connection with renal function tests, however, one must remember that notable increases in the concentrations of urea, uric acid, creatinine, nonprotein nitrogen, etc., occur only with renal failure. Mild hyperazotemia may result from metabolic disturbances and shifts in water balance without renal failure. Thus minor fluctuations in concentration are difficult of interpretation. In "compensated" nephritis the "blood chemistry" fails to measure the *reduced reserve*.

As urea retention is characteristic of renal failure leading to clinical uremia, special emphasis has been placed on the study of urea excretion. Multiple attacks on this problem over more than twenty years have gradually evolved the urea clearance test. By "blood urea clearance" is meant the number of cubic centimeters of blood cleared of urea by renal secretion per minute. The formula for expressing this is  $\frac{UV}{B}$ , where U is the concentration of urea in the urine, V the volume of urine in cubic centimeters per minute, and B the concentration of urea in the blood. When the volume of urine is less than 2 cc. per minute the urea secretion is depressed by the square of the reduction in volume and thus, when less than 120 cc. are excreted per hour, the formula must read  $\frac{U}{B} \sqrt{V}$ . This latter is termed "standard" clearance, the former "maximum" clearance. The average standard normal clearance is 54 cc. blood cleared per minute, the average normal maximum clearance is 75 cc. blood per minute.

Careful studies<sup>10</sup> reveal that the urea clearance is a very accurate guide to the effectiveness of glomerular function. In severe nephritis this test gives clear evidence of change for the better or worse. In milder instances the test is not so sensitive in revealing lowered reserve as the concentration test.<sup>1, 7</sup> It is not a "stress test" as carried out at present. It is physiologically sound and not so complex as appears at first thought. A sample of blood is drawn immediately after the patient voids and then one hour later the specimen of urine is collected.

Innumerable substances have been introduced for use in measuring renal excretory efficiency, but thus far **phenolsulphonphthalein** has proved most satisfactory. This nontoxic dye is extraordinarily specific for kidney tissue; 98 per cent of injected dye can be reclaimed from the urine and kidneys of dogs.<sup>11</sup> The dye is secreted largely by the proximal convoluted tubules. The procedure for the test varies in different clinics, chiefly in the time interval at which specimens are collected. Here the routine is to collect urine specimens one, two and three hours after the intravenous injection of exactly 1 cc. of the dye solution (ampule). Some advocate shorter time intervals, but then it is often necessary to catheterize the patients and this is best avoided. The amount of dye excreted is determined colorimetrically in an alkaline dilution of the urine.

The "phthalein" test has deserved popularity. It is not, however, as sensitive to minor changes in function as the concentration test. The promptness of secretion is important. It is particularly adaptable to unilateral investigation of the kidney function; with ureteral catheters in place it is possible to determine the dye output on each side separately. Two readings at fifteen-minute intervals suffice. In rare instances some metabolic quirk causes chemical destruction of the dye within the body. If the urine contains no dye after injection, this is thus no proof of renal failure. With coincident hepatic disease the urinary output of the dye is increased. All these and other variables must be considered in interpreting the results of this test.

Very recently a new test substance has received clinical

trial. Sodium ferrocyanide is secreted solely through the glomeruli.<sup>12</sup> This test procedure is still in an experimental stage,<sup>13</sup> but various studies show a close parallelism between the ferrocyanide excretion and the urea clearance.<sup>14</sup>

As stated before, we have no adequate method for detecting early depression of the renal activities in maintaining the acid-base balance of the body. Gross shifts toward acidosis or alkalosis are measurable by determining the CO<sub>2</sub> combining power of the blood (van Slyke). An intensive clinical study of this aspect of the problems of nephritis is needed.

#### CLINICAL APPLICATION OF TESTS

There are so many clinical applications for renal function studies that it is impossible to do justice to the subject here. Some of the indications we have mentioned previously. Four clinical examples may serve to illustrate certain points of interest.

**Case I.**—The first patient, Miss E. H., is a girl of fifteen years, who was first admitted to the hospital about a year ago. The primary complaints were habitual exhaustion and undernutrition. Vertigo, recurrent headache, increasing asthenia followed a coryza with cough two months prior to admission. The cough persisted. She denied previous illness. Her menses started at thirteen, but had been increasingly scant the last six months. The intern suspected tuberculosis because of her marked undernutrition and the persistence of some cough. Examination revealed a tall, very thin, pale girl appearing much more mature than her age. Her physique was typically Stiller in type. The chest was resonant throughout, with a few fine crepitant râles scattered diffusely through the pulmonary fields. These râles did not persist after intentional coughing. The heart was not enlarged and no murmurs were heard, but the second aortic sound was accentuated and ringing in character. The intern had not determined her arterial tension "because she was still a child." Her blood pressure was found to be 150/100. Specific inquiry revealed that she had been ill for

four months with a very severe attack of scarlet fever three years previously. You will recall that the girl had told the intern she had had no previous illness. This misstatement was not deliberate or with intent to mislead; she had merely not associated "previous illness" with her scarlet fever. To get an accurate story it is necessary to be specific in questioning.

Urinalysis revealed 40 mg. albumin per 100 cc. urine, granular casts and some erythroplastids. The x-ray film of the chest was normal. Anemia was marked: hemoglobin 68 per cent (Newcomer), red blood cells 3,140,000, white blood cells 8550. The diagnoses were:

1. Chronic nephritis (postscarlet fever).
2. Early, spastic hypertensive arterial disease.
3. Anemia, secondary.
4. Undernutrition.
5. Recent coryza precipitated symptoms.

These, however, were purely qualitative diagnostic impressions. Further study was needed to reveal the extent of renal function impairment. The following data were elicited:

1. Renal concentration test:

Maximum specific gravity = 1.021

(repeated) specific gravity = 1.020

2. Phenolsulphonphthalein excretion:

60 minutes 60 per cent

120 minutes 20 per cent

Total 80 per cent

3. Urea clearance (standard): 56 cc. blood cleared per minute.

4. Glomerular function test (sodium ferrocyanide):

30 minims	9.3 per cent	Normal = 12 to 17 per cent
60 minims	7.9 per cent	8 to 12 per cent

Total	17.2 per cent	20 to 30 per cent
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The function tests revealed: (1) impaired renal reserve (lowered maximum concentration); (2) normal "phthalein" output and urea clearance; (3) reduced glomerular function.

We cannot discuss therapy here, but, with this girl, the

most urgent indication was to correct the severe anemia. It is unjustified to expect rehabilitation and repair of tissues receiving an inadequate blood supply. Since then the patient has reported a number of times for re-evaluation of the situation. The thoracic findings cleared up promptly. Six months ago the following data were obtained:

1. Hemoglobin 76 per cent (Newcomer), red blood cells 4,180,000.

2. Arterial tension 124/84.

3. Renal concentration test:

Maximum specific gravity = 1.023.

4. Urea clearance (standard): 59 cc. blood cleared per minute.

5. Glomerular function (sodium ferrocyanide) output:

30 minims 14.3 per cent

60 minims 14.3 per cent

Total 28.6 per cent

The present findings are:

1. Hemoglobin 92 per cent (Newcomer), red blood cells 5,260,000.

2. Arterial tension 122/74.

3. Renal concentration test:

Maximum specific gravity = 1.024.

4. Urea clearance (standard): 58 cc. blood cleared per minute.

5. Glomerular function (sodium ferrocyanide output) continues normal.

The renal function tests on this case served not only to confirm and prove the original diagnosis and show that depletion of the functional reserve was as yet small, but also made possible proof that the renal function has returned to normal in the last year with correction of the anemia. It is interesting to note that the arterial tension also returned to normal with the improvement of the blood picture.

**Case II.**—The second case presents a somewhat different problem. A business executive of fifty-eight years has known

of his hypertension for fifteen years; it was discovered shortly after a severe streptococcal sore throat. At that time hematuria was marked. At present the chief complaint is that of typical anginal thoracic pain on either exertion or excitement. This has been getting worse. Hypertension has been responsible for three deaths in his family. The electrocardiogram reveals left ventricular preponderance and myocardial damage. His arterial tension is 220/120. Upon inhalation of amyl nitrite the arterial tension falls to a minimum of 130/80<sup>1, 15</sup> revealing that the arteriolar narrowing is largely spastic rather than arteriosclerotic. The urine contained many casts and 15 mg. albumin per 100 cc. The diagnosis included:

1. Hypertensive arterial disease.
2. Angina pectoris.
3. Oral sepsis.
4. Nephritis, degree undetermined.

Renal function tests revealed:

1. Renal concentration test:

Maximum specific gravity = 1.024.

2. Phenolsulphonphthalein excretion:

60 minims	50 per cent
120 minims	17.5 per cent
Total	<u>67.5 per cent</u>

3. Urea clearance (maximum): 71 cc. blood cleared per minute.

4. Glomerular function (sodium ferrocyanide excretion):

30 minims	12.8 per cent
60 minims	20.3 per cent
Total	<u>33.1 per cent</u>

These data demonstrate that despite the suggestive history of a streptococcal infection followed by hematuria and severe hypertension, the renal function is essentially normal. Renal impairment, therefore, is not an etiologic factor in this instance of hypertensive arterial disease. The patient should be treated as a cardiac problem, not renal.<sup>1</sup>

**Case III.**—This third case, W. J., was a young man of twenty-two years, who entered the hospital for renal function study. He was known to have nephritis. This dated from scarlet fever at five years of age. He had felt well until three months before admission. He complained bitterly of persistent headache, nausea, vomiting, dyspnea and cough. He was pale and very breathless. The significant findings were:

1. Hemoglobin 48 per cent (Newcomer), red blood cells 2,690,000, white blood cells 9,750.

2. Arterial tension 196/130.

3. Renal concentration test:

Maximum specific gravity = 1.011.

4. Urea clearance (maximum): 4 cc. blood cleared per minute.

5. Phenolsulphonphthalein excretion:

60 minims           — 5 per cent

120 minims         — 5 per cent

Total                ± 8 per cent

6. Glomerular function test (sodium ferrocyanide): only trace recovered.

7. Blood chemistry: nonprotein nitrogen, 184; urea nitrogen, 60; creatinine, 8.7; CO<sub>2</sub> combining power, 33.6 volumes per cent.

Such findings are typical of uremia. The fundamental failure lies in the inability of the kidneys to concentrate the urine. Despite the dehydration due to his vomiting (more severe dehydration than in the ordinary test) the maximum concentration was but 1.011. The prognosis was black; the hyperazotemia, profound anemia and acidosis reveal that the end was not far off. His parents were informed that his life expectancy was but four to eight weeks; no therapy could restore his lost renal function. He died at home six weeks later.

**Case IV.**—This last case example is perhaps the most instructive of all. When Mrs. A. S., twenty-six years old, reported for her first examination to the prenatal clinic she was



six months advanced in her second pregnancy. There had been, unfortunately, no previous prenatal care. She presented no complaints but her urine contained 60 mg. albumin per 100 cc. and her arterial tension was 160/100. No edema was demonstrated. She stated that her first pregnancy terminated prematurely with a rapid, violent labor and delivery of a stillborn infant. As the first pregnancy and delivery was without medical attention, our information depended entirely upon her statements. She denied ever having had scarlet fever, diphtheria, or rheumatic fever, but admitted a severe and prolonged sore throat eight years ago.

The problem presented was one of differentiating the possible reasons for this patient's hypertension and nephritis. The previous history suggested hypertension in her first pregnancy with abruptio placentae, accounting for the violent labor and death of the fetus. Such would be typical of preexistent nephritis exacerbated by pregnancy.<sup>3</sup> On the other hand, the situation was compatible with preeclampsia.

The Wassermann reaction was negative. Her arterial tension fell from 162/104 to 140/90 with the amyl nitrite test.<sup>15</sup> The blood had a hemoglobin content of 62 per cent (Newcomer), red blood cells 3,120,000; white blood cells, 7400. The renal function tests revealed:

1. Renal concentration test:

Maximum specific gravity = 1.017.

2. Urea clearance (maximum): 68 cc. blood cleared per minute.

3. Phenolsulphonphthalein excretion:

60 minims	45 per cent
120 minims	25 per cent
Total	70 per cent

4. Glomerular function (sodium ferrocyanide):

30 minims	8.4 per cent	Normal = 12 to 17 per cent
120 minims	6.1 per cent	8 to 12 per cent
Total	14.5 per cent	20 to 30 per cent

These studies demonstrate: (1) moderate arteriosclerosis; (2)

marked impairment of functional reserve in concentrating the urine; (3) impaired glomerular secretion; (4) normal urea clearance; (5) phenolsulphonphthalein excretion delayed; (6) severe secondary anemia. These facts are wholly compatible with a diagnosis of chronic nephritis and hypertension, exacerbated by pregnancy, but incompatible with preeclampsia. Although the renal function tests revealed no severe damage, the embarrassment was increased greatly by the added load placed upon the kidneys by pregnancy.

The patient was kept under observation in the hospital. Her blood pressure rose *gradually* to 185/120. Every effort was made to treat the anemia and her hemoglobin content rose to 79 per cent. Just before eight months, when the fetus was reasonably viable, she was delivered by cesarean section and sterilized. The placenta contained numerous small infarcts. Following delivery the arterial tension has remained high; now, six months postpartum, it is 150/96. The future course, typical of this type of nephritis in pregnancy, will be one of slow but persistent progression of the hypertensive disease and nephritis. The baby survived.

#### SUMMARY

Renal function tests are not only useful but necessary for proper study and evaluation in clinical situations involving the kidneys. They serve to measure the renal reserve capacity, to localize the site of greater injury and to reveal changes in the extent of renal damage.

The renal concentration test, which is the simplest to perform, is thus far the most sensitive indication of depletion in functional reserve. The urea clearance test is a more accurate guide to changes in function in advanced nephritis. Phenolsulphonphthalein excretion is grossly impaired only when damage is extensive. The glomerular function test with sodium ferrocyanide is still experimental; further study indicates that there is a real place for this procedure in our diagnostic armamentarium.

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## CLINIC OF DR. DAVID A. HORNER

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### DIAGNOSIS AND MANAGEMENT OF ANTEPARTUM FETAL DEATH

THE fetus like the fruit of a tree usually starts auspiciously, goes through a period of normal growth, and finally reaches maturity in a healthy normal condition; but like the fruit of a tree, it may encounter various pathological conditions which interfere with this normal development so that it may become deformed or die at any stage before reaching maturity. I shall consider only the recognition of the death of the fetus or embryo, and for various reasons which you will see, I shall divide these deaths into two groups: first, those occurring before quickening; and secondly, those occurring from quickening to term.

The diagnosis of life or death of an embryo or fetus is always of great importance. For the patient it may involve moral, physical, economic, and other problems but for the physician it becomes a problem of diagnosis to be approached with great caution, yet without fear. The subsequent conduct of the case naturally depends on the decisions reached by him.

**Before Quickening.**—A pregnant woman reporting shortly after conception shows practically no physical changes. We may have only the data that a menstrual period has been missed. In a woman of childbearing age, heretofore always regular, the significance of that statement is that she is pregnant. As the pregnancy develops, certain signs and symptoms with which you are all familiar become manifest, for example: nausea and vomiting, enlargement of the uterus, discoloration

of the vagina, breast changes, etc. All of these bear out that conclusion. Needless to say, the Aschheim-Zondek test is positive. Should death occur to the embryo in this early stage, one notes a change in these symptoms and signs. The breast symptoms disappear, nausea and vomiting cease, the uterus does not grow, in fact it may decrease in size, there may be brownish stains appearing on the clothing, vaginal coloring returns to normal, and the Aschheim-Zondek is negative. If this return to normal is noted by the physician who has seen the positive signs and symptoms of pregnancy in his patient, there should be little hesitation in arriving at the conclusion that the embryo is dead.

Death of the embryo usually has a salutary effect on the woman who suffers from excessive vomiting and this improvement alone is diagnostic. Should the patient report for the first time after the death of the embryo, when pregnancy signs and symptoms are negative, and the attendant has nothing for physical comparisons in the patient, the diagnosis still can be made by a careful history which shows that symptoms of pregnancy were recently present and have since changed. A uterus slightly larger than normal may or may not be significant. A negative Aschheim-Zondek under such conditions is of little value. Dr. Rezek of the Medical Department of the University of Illinois has recently shown that follicular changes in the ovaries of rabbits are characteristic when the urine of women with dead embryos or fetuses is injected as for the Aschheim-Zondek test.

Until now it would appear that I am referring only to pregnancy in the uterus. But the statements just made apply with equal value to pregnancies which have died in the tube. It applies also to pregnancies in the abdominal cavity which primarily started there and to pregnancies which began in the tube and later became tubal abortions, whose disrupted circulations resulted in death.

I have yet to find a train of symptoms which gives a clue to the diagnosis of embryonic death. Statements are made by DeLee and Litzman that they have noted a clinical syndrome

of malaise, anorexia, headache, loss of weight, chilliness, foul taste, bearing-down sensations, and increasing invalidism. This has not been my experience. These symptoms have not appeared characteristically in the hundreds of early intra-uterine and extra-uterine deaths investigated even when the dead products of conception were retained for many months. Authors have written up cases retained in the body for many years without mention of a single symptom in the above list. However, when infection complicates matters, such a picture, plus fluctuating febrile temperatures is the rule. All cases of extra-uterine deaths studied came to the operating table, some diagnosed as extra-uterine pregnancies and some not; the indication for the operation was the persistent symptom of pain.

Most intra-uterine early pregnancies are expelled spontaneously within a short time after death of the embryo and are treated as abortions, without diagnosis of life or death. Tubal abortions resulting in the death of embryo are numerous. It is wise, however, not to consider all of them dead. Evidence that they need not all be removed exists in the fact that many useful citizens are alive today although they were at one time in their lives nothing less than tubal abortions. They continued to thrive in their new surroundings among the intestines and developed to maturity. Laparotomy, of course, was necessary to deliver them.

Tubal abortions which die or those arriving at maturity and which die undelivered, frequently remain in the abdomen for many years without sufficient symptoms to require laparotomy. The Aschheim-Zondek in such cases should be a useful guide. In the absence of sufficient symptoms for operation, it indicates a *laissez-faire* policy, except when alive and approaching maturity. Radicals believe that such abnormal pregnancies are better removed immediately on diagnosis, regardless of the condition of the fetus, because of potential difficulties to be encountered later.

**From Quickening to Term.**—During this period there are present other elements in the fetus which have great value in determining its life or death. First in importance is per-

ceptible movements of the living fetus. A mother, who has once felt them during pregnancy, quickly misses them on their cessation. The history of such a change is significant but in itself not sufficient to establish the diagnosis of death. Very often I have been able to palpate fetal movements while the patient is on the table, and have the patient entirely unaware of their existence. However, such a finding is subject to error and requires corroboration by other methods.

The fetal heart tones are characteristic of life during this stage and are often heard distinctly as early as the beginning of the fifth month. Falls, with his intravaginal stethoscope, claims to hear them earlier than that. When once heard, the diagnosis of life of the fetus is assured; however, one of twins may die, its heart tones naturally disappearing, while the heart tones of the surviving fetus continues. The death of its twin remains unrecognized until delivered.

The disappearance of all heart tones, when they have once been heard by the physician in attendance, definitely points to the death of the fetus. Another important sign, even of greater value than the disappearance of fetal heart tones, is the indescribable silence over the abdomen, which one obtains when the fetus is dead. You have all probably encountered this stillness in the presence of fetal death. It is a silence which can literally be "heard," because of the way it stands out in auscultation of the abdomen.

A negative finding of considerable importance is the improvement in the patient's condition when there is associated toxemia. With the death of the fetus, hyperemesis improves and often disappears; edema is lessened and blood pressure drops. However, such findings cannot be considered 100 per cent positive. Corroborative evidence must be added.

In 1921, I brought out before the Chicago Gynecological Society, the fact that the x-ray can be used in determining this condition. World-wide corroboration of my findings and further experience with the x-ray, have convinced me that we have here means of obtaining conclusive evidence that fetal death really exists. As you have all noted in cases of stillbirth, the brain



is practically the first organ in the fetus to undergo degeneration. It follows then that the loose, enclosing skull covering the fetal brain collapses down on its shrinking contents, and when *x*-rayed, shows changes in contour characteristic of death. I have demonstrated this with a fetus externally on the first day following death, and intra-uterine as early as the third. Overriding of the skull bones with cephalic asymmetry are positive signs of intra-uterine fetal death and may be observed even before surface maceration.

There are those who require a longer time in order to be assured of such a diagnosis roentgenologically. They base their opinions on a comparison of the age of the fetus as shown by *x*-ray, and compare it with the age calculated from the date of the last menstruation. The difference in size indicates the duration of death. The chief objection to this method is that death must be present for a sufficient length of time to show this disparity in size and age. Elements of error based upon the fallacies of technic and calculation are always present.

Repeated *x*-rays at two-day intervals are found to be revealing not only in the changes which occur in the fetal skull, but the constant fixed posture maintained by the fetus throughout the period of observation. Such findings as angulation of the fetal spine and collapse of the thoracic cage are also considered of value but, I should say, only when there are associated skull changes. I believe these findings are present only in the utmost degrees of maceration and disintegration, and are secondary to those changes which occur in the fetal skull.

There are some investigators who claim that overriding of the fetal skull may appear in the living fetus before birth. I grant that, but only after the onset of labor pains or difficult lightening. Dr. Maurice Blatt shows the picture of a living microcephalic idiot, with overriding of the skull bones several years after birth. I mention this merely to point out that there are possibilities of error. Dependence on one sign alone is full of risk. A new life may be at stake as well as a reputation: therefore, I advise consultation for a division of responsibility.

All data must be assembled and studied before drawing conclusions and making the final diagnosis. The subsequent treatment may then be pursued without hesitation.

All too frequently we encounter patients in whom this unfortunate complication has occurred more than once. Habitual abortion or habitual fetal death then really becomes a serious problem. The patient with one accident usually becomes reconciled if her reproductive years lie ahead of her, but if no live birth results, she considers her losses more and more with the passing years and each loss more tragic than the one before. In such cases the internist also plays an important rôle in locating the etiologic factor.

The therapeutics of fetal death within the mother consists in removing the products of conception. In early uterine pregnancies before quickening the one- or two-stage abortion is indicated. Intra-abdominal pregnancies in this stage may remain quiescent and need not be hurriedly laparotomized; they may even be left alone. When necessary, those pregnancies beyond quickening should be removed by midline laparotomy just like ectopic pregnancies. The intra-uterine cases usually abort but if evacuation is desirable preliminary bags are employed (1 cm. for each month of pregnancy—five months, 5-cm. diameter; seven months, 7-cm. diameter, and so on). Following the expulsion of the bag, manual or instrumental removal can then be undertaken safely.

Hysterotomy, usually by the vaginal route, can be performed without great jeopardy to the mother, but such extensive surgery for this complication is rarely undertaken. The abdominal hysterotomy is too formidable a risk as the dead fetus and secundines are undergoing degeneration in the uterus and are a potential source of infection.

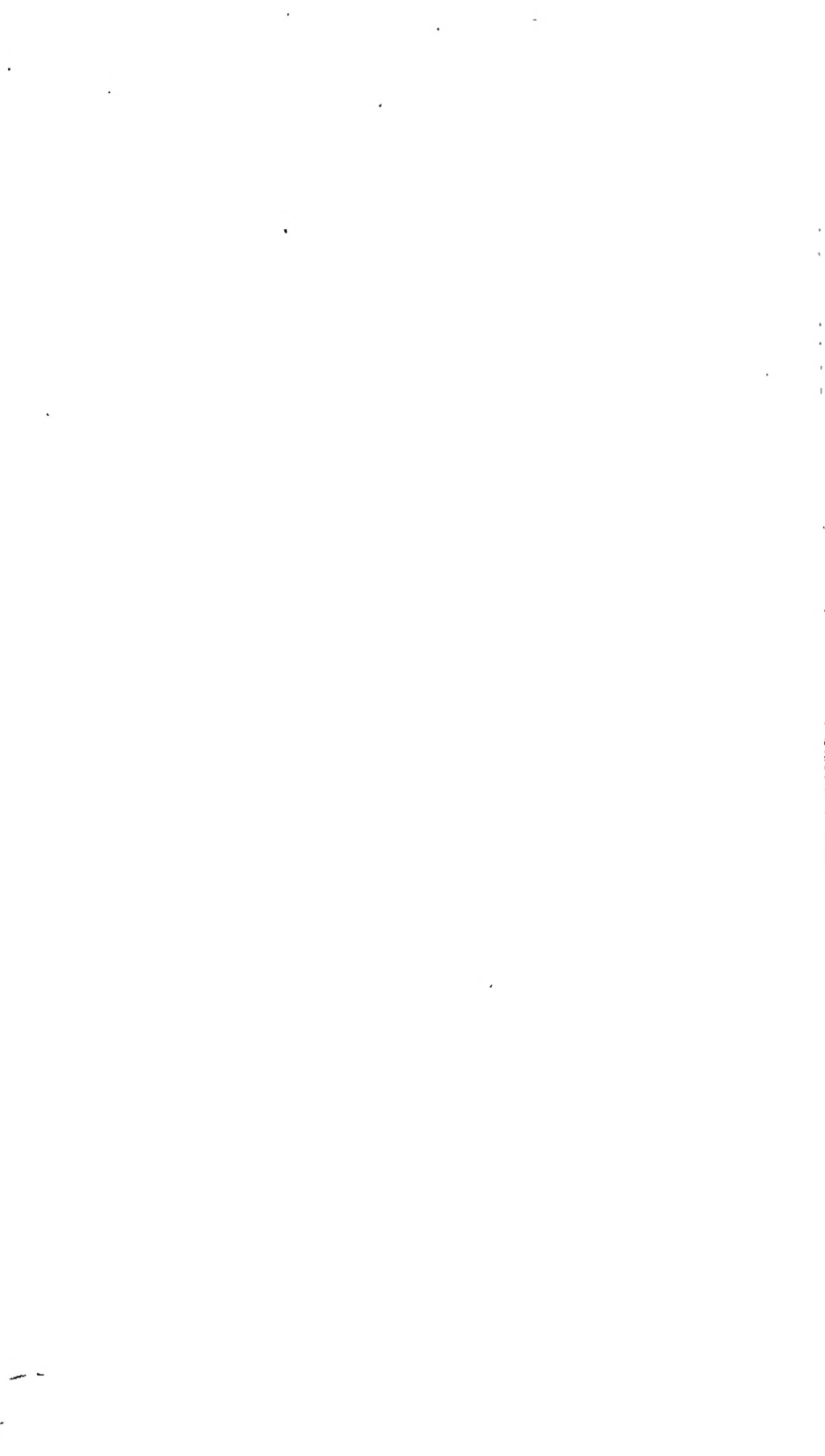
An intra-abdominal pregnancy which dies from quickening to maturity, as a rule, is sterile and may be considered a foreign body. Its hasty removal may lead to serious complication—especially if the placenta is attached to vascular structure—which themselves cannot be removed. If operation is performed the placenta should not be removed if it is attached

to intestines or other important structures. Ligation of the cord with catgut or silk close to the placenta with usual closure of the abdomen is sufficient.

One case with which I am familiar went to term with a normal-sized infant. Attempts to induce labor by bags were attempted on several occasions and given up because of technical difficulties. The pregnancy turned out to be intra-abdominal. The attending physician became ill and nothing was done for the patient for several years. Laparotomy was ultimately performed with removal of a cystic mass which contained all the bones of a normal-sized term fetus. The whole mass was then no larger than a grapefruit, pedunculated and readily removed. The site of the placenta could not be found as the rest of the abdomen was normal. The placenta was completely absorbed. A formidable operation became an easy one.

I mention this case only to show the harmlessness of allowing a dead fetus to remain unremoved. Each case, however, must be given individual consideration and in the absence of special indication should be treated with slow and deliberate methods.

For habitual death of the fetus at term, we have only the premature induction of labor. Associated diseases as syphilis or nephritis, of course, must receive appropriate treatment. When the cause is unknown, the handicap becomes greater. The high mortality rate of infants delivered by induction of premature labor makes one wonder if this operation should not give way to that of premature abdominal cesarean section.



## CLINIC OF DR. EDWARD A. ALLEN

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#### DIAGNOSIS AND TREATMENT OF PERSISTENT VAGINAL DISCHARGE

THE diagnosis and treatment of vaginal discharges is still frequently based on inadequate examinations and failure to establish definitely the etiological factor. I should like this morning to present several patients whose histories reveal the more common diagnostic errors and discuss with you how we may avoid them.

This little girl of eleven years illustrates very well the importance of an accurate history of the complaint, evaluation of the sequence of events and the gratifying results obtainable with simple procedures. Four years ago the mother of this youngster noticed more than the normal amount of discharge on the child's underclothing. The vulva was irritated and when the mother questioned her the little girl admitted that there was some discomfort during urination. Immediately the mother's suspicions were aroused and when further questioning elicited the information that her daughter had been playing during school recesses in an abandoned building near the school her fears were increased. When she learned further that several older boys also frequented the playhouse, suspicions turned into certainty that the discharge must be venereal in origin. Prompt medical advice verified this diagnosis and then began the long period of treatment for gonorrheal vaginitis. Four years of psychic trauma both to this child and her mother have followed. Due to the father's occupation, several changes in residence have been made during this time. In each new home the original diagnosis has been taken for granted and the treat-

ment continued. Four weeks ago the discharge began to change color and became brown. When we saw her first, two weeks ago, the discharge was profuse and contained gross blood. It was at once evident that we were not dealing with a gonorrheal vaginitis unless constant reinfection had occurred, because gonorrhea is not a chronic disease. This condition, as in the adult, runs its course and disappears even in the absence of treatment.

Finding the gonococcus in the vaginal secretion over long periods of time has, in our experience, always gone hand in hand with a definite history of reinfection. Methylene blue and Gram stains of this secretion failed to reveal the presence of the gonococcus. The complement fixation test was negative. On rectal examination an indurated area could be felt in the vagina, especially on the right side. This induration extended from the vaginal vault to the hymenal ring. With the patient in the knee-chest position, air was allowed to distend the vaginal canal. By carefully inserting this small Kelly cystoscope containing the proper illumination, a thorough inspection of the vaginal walls could be carried out without anesthesia. This large hairpin which I have was found with one leg of it almost covered with granulation tissue and grown into the right vaginal wall. Five minutes of ethylene anesthesia was sufficient for the removal of the foreign body. The mother says today that the discharge has entirely stopped. The patient either does not remember when or by whom this foreign body was inserted or still wilfully denies any knowledge of its presence.

Only about one half of the vulvovaginitis in children is caused by the gonococcus. The remainder are of nonspecific origin and in about 10 per cent of instances are caused by foreign bodies. In our clinic here in Rush Medical College devoted to vulvovaginitis, we have found other hairpins, safety-pins, shoe buttons, balls of cotton, beans, and a buffalo nickel. Small articles of almost every description have been reported in the literature as a cause of vulvovaginitis. If the gonococcus is not clearly demonstrable in the smear, or if

excessive secretion continues for long periods of time, rectal examination may at once reveal the diagnosis. Inspection through a vaginoscope with the patient in the knee-chest position can be carried out usually without anesthesia even in babies, if proper care is exercised in insertion of the instrument. This procedure should never be omitted in the diagnosis of nonspecific vulvovaginitis.

This patient illustrates very well a type of vaginal discharge that has become increasingly frequent in the last few years. The history of her complaint is quite characteristic. Three years ago the patient consulted her physician concerning a moderate leukorrhea. At that time an erosion of the cervix was found and an extensive radial cauterization of the cervix was done. For about eight months following this treatment the patient was free from discharge. The return of the discharge was abrupt and has recurred intermittently during the past two years. The discharge now present has contained small amounts of blood during the last three weeks. The patient complains of considerable burning in the vagina and smarting about the introitus.

Pelvic examination reveals normal pelvic findings except that the cervix seems to be slightly enlarged and succulent. As we view the cervix through this bivalve speculum, you will notice the distortion of the external os and here on the right side its lips are glued together by thin adhesions. The further distortion of the cervical canal can be determined with this soft probe which we will introduce gently as far as the internal os. You will notice, when the probe is withdrawn, a rather large amount of thick leukorrheal discharge tinged with blood escapes. This fluid has been pent up behind the partial or at times probably complete stenosis of the cervix. Increased tension has at times become sufficient to overcome the obstruction and this explains the intermittent character of the discharge. The damming back of secretion, of course, predisposes to infection, maceration of the endocervix and as a result increased secretion which now has become streaked with blood. We shall gently dilate this cervix with smooth graduated

dilators to overcome the obstruction and prevent as nearly as we can further trauma to this already damaged cervix. Subsequent contraction of this scar tissue, however, is the general rule and repeated dilatations are usually necessary until the canal of the cervix is completely healed but still patent enough to permit free drainage. We do not favor extensive cauterizations of the cervix and especially those which involve the cervical canal. Clinical cure can usually be obtained by wiping off the external erosions of the cervix with the nasal snare cautery point without invasion of the cervical canal.

I should like at this time to present to you 3 additional patients whose clinical histories of vaginal discharge are almost identical. The etiological factors, however, are different in each individual. These patients represent that large group of individuals having nonspecific vaginitis which all of us encounter in our daily practice. They are very important not only as gynecological diseases but, since they may involve the urinary tract, gastro-intestinal tract, perianal region and, in the male, the prostate, they become of general interest.

These 3 patients all relate this similar history: following the last menstrual period a profuse vaginal discharge began. This was accompanied by pronounced burning and itching in the vagina and about the external genitalia; lumbosacral backache and a bearing-down sensation in the pelvis have become more severe daily. Frequency of urination has been increased, and in this first patient whom we shall now examine nocturia has become a very distressing symptom.

You will notice here as we inspect the vulva and perianal region that the skin is reddened and excoriated. The superficial layers are slightly macerated due to the constant irritating discharge that is present. This discharge is watery and the small bubbles contained in it at once give us the clue to its origin. Therefore, before bimanual examination is undertaken, specimens of this discharge will be obtained by collecting it in the posterior blade of the speculum. Contamination of this secretion with examining jelly, and especially glycerin, would vitiate our results. In like manner, recent vaginal medication



or even a plain water douche may render immotile the flagellates which we confidently expect to find here. It can readily be seen that this discharge does not resemble the yellowish puslike discharge caused by the gonococcus. It has a greenish tinge and is more watery and bubbly in consistency. However, we will make the usual smears for subsequent staining as occasionally gonorrhea and *Trichomonas vaginitis* occur together. If we place a small drop of this secretion on the slide and cover it with a coverslip, a thin layer of material results.



Fig. 19 - *Trichomonas vaginalis* as seen in the unstained secretion. The flagella are usually bipolar in arrangement.

If this layer remains too thick for satisfactory microscopic examination, slight pressure on the coverslip or the addition of a drop of normal saline will suffice to thin it. Now under high dry magnification and reduced illumination a careful search will be made for motile organisms. This motion, as you see, is of a whipping, lashing character which violently agitates the cellular debris and clumps of coccoid organisms which are present in large numbers. These motile organisms are flagellates called *Trichomonas vaginalis* (Fig. 19). They are found

in patients presenting symptoms of vaginitis many times more frequently than is the gonococcus. They cannot be identified in the usual stained preparation but should be recognized by their motility and identification of the flagellates while in motion. Special stains have been advised by several investigators



Fig. 20.—The marked bilateral dilatation of the ureters in this patient was apparently the result of the trigonitis. The typical edema about the ureteral orifices was very marked.

but, at least in our experience, the fresh secretion remains the best means for identifying these organisms. You will notice that this secretion bathes the external genitals. If we depress the posterior wall of the vagina the external urethral orifice gapes and the secretion actually seems to be aspirated into it. This may well account for the typical urethritis found so fre-

quently associated with this infection. Extension upward into the bladder seems to be almost a foregone conclusion. We must, however, bear in mind the possibilities of a direct extension from the adjacent anterior fornix of the vagina. About one half of these patients present a typical trigonitis. When viewed through the cystoscope these areas are usually confined to the urethra and trigone and not infrequently involve the ureteral orifices. In this x-ray film (Fig. 20) you will see a bilateral hydronephrosis for which we could find no other cause than the marked edema about the ureteral orifices. This patient was relieved of all of her symptoms following treatment of the *Trichomonas* in the vagina and refused to allow even a follow-up intravenous pyelogram. This edematous area in the bladder mucous membrane is fluffy, pale, and in some areas resembles a leukoplakia. Scattered over the surface of the lesion but more pronounced around its periphery are many small petechial hemorrhagic spots. These spots suggest the presence of the streptococcus. We have isolated from the catheterized urine of these patients and also from tissue removed with the suction curet large numbers of hemolytic streptococci. Histological examination of these bits of bladder mucosa reveal a thickening and vacuolization of the squamous cell layer.

When the excess secretion is wiped from the vaginal walls the mucous membrane is red and edematous. Scattered everywhere, but particularly in the anterior fornix, are many petechia-like spots similar to those we have just described in the bladder mucosa. The descriptive term of "strawberry vagina" has aptly been applied to this condition. Biopsy specimens removed from these hemorrhagic areas reveal a subepithelial infiltration with leukocytes and coccoid organisms. Invasion of adjacent tissues, such as the bladder and parametrium by means of the lymph or blood vessels, may offer a logical explanation of the spread of the infection. That the infection does spread we are quite certain. We have observed definite clinical and palpatory evidence of invasion developing in many of these patients for which no other explanation than the vaginitis could be found. Numerous patients have begun to bleed

profusely or intermittently soon after the onset of the vaginitis. The increased blood loss has been controlled as soon as the vaginitis has been adequately treated. During the course of the disease several women have developed severe pain and rigidity in the lower quadrants accompanied by elevations in temperature and the leukocyte count. Pelvic examinations at this time revealed tender swellings in the region of the adnexa which had previously been normal to palpation. We have isolated the typical streptococcus, which is regularly associated with *Trichomonas vaginitis*, from the acute swellings of the Bartholin gland found in several of these patients. Erosions of the cervix which are frequently found in conjunction with *Trichomonas vaginitis* may heal completely when the vaginitis has been cured. However, it may be necessary in the later stages of the treatment to lightly cauterize these lesions for the complete eradication of the vaginal infection. Cauterization should not be done in the acute stages as acute pelvic cellulitis may be the result.

The treatment of *Trichomonas vaginitis* is still empirical. Good results can be obtained in from 50 to 80 per cent of the patients with any one of several procedures. The remaining 20 to 50 per cent recur at intervals, often for many years. Until further investigation clears up the primary mode of infection and probable methods of reinfection, better results in treatment will likely not be obtained. The fundamental rules governing almost all of the generally accepted plans of treatment are the same. The vaginal walls and introitus should be scrubbed free from secretion either with green soap or a gauze sponge. These surfaces should then be sprayed or painted with medicinal substances which are not too irritating to the vaginal mucous membrane. These medicaments may be in solution, powders, pastes or in the form of vaginal suppositories. The substances most commonly advised are the dyes, as methylene blue either in aqueous solution or mixed with glycerin. picric acid  $\frac{1}{2}$  per cent in solution or contained in suppository form, drying powders such as kaolin or fuller's earth alone or in combination with alkalis such as sodium bicarbonate. Lac-

tose and citric acid are more recent additions to the list. Many of these powders contain one of the arsenicals such as stovarsol or carbarsone in proportions of 2 parts to 7 parts of the powder. Lactic acid forms the basis of several of the jellies or pastes in common use but has a probably wider use in the vaginal douche and can be used by the patient daily. The powders must be applied or insufflated by the physician, although recent tablet forms are receiving wider attention.

This patient will be placed on the following treatment: the vagina and external genitals will be cleansed with tincture of green soap and then thoroughly dried with gauze sponges. Through the speculum we can then spray the walls with this powder composed of 2 parts of stovarsol to 7 portions each of sodium bicarbonate and kaolin. The distribution of the powder should also include the introitus. We have found this little spray can, which is ordinarily used for insect powders and obtainable at any drug store for 10 cents, very satisfactory. The patient should be instructed to protect herself with a pad as the powder liquefies and produces a profuse discharge. Tomorrow morning and each morning thereafter the patient should take a 2-quart warm water douche to which has been added 1 drachm of lactic acid. These treatments should be continued daily for at least one week. At the end of that time the patient may carry on her treatment at home by inserting into the vagina upon retiring a vaginal suppository containing 1 per cent picric acid. The excess material from the suppository should be removed the following morning with the lactic acid douche. Following the next menstrual period the powder insufflations should be carried out again for a few days because at this time recurrences seem most likely to occur. This general scheme should be followed for at least three months, gradually decreasing the frequency of medication. The douche should be sterilized from time to time as we have encountered several recurrences which have unquestionably been on this basis. Continued effort to increase the general resistance by rest, high caloric and vitamin diets will be advised. The husband will, if possible, be examined by two tests, one for the presence of *Trichomonas* or a nonspecific organism.

The second patient of this series you will notice presents the same clinical symptoms with the exception of urinary distress. Careful inspection of the external genitals, however, reveals an entirely different picture. The introitus is reddened and edematous with tiny areas here and there where the superficial layers of the skin have been removed by scratching. The amount of external discharge is entirely within normal limits. If we, however, inspect the vaginal walls we see that they are



Fig. 21.—The typical branched, segmented mycelia of yeast stand out clearly in this specimen stained with the Gram stain. The bud forms are characteristic enough to warrant identification even in the absence of the mycelia.

covered everywhere with a thick, cheesy, almost membrane-like material occurring in plaques. When these plaques are wiped away, a raw surface is found beneath them and occasionally minute bleeding points appear. The appearance of these vaginal walls is very similar to the condition found in the mouths of babies with thrush. We might well speak of this condition as vaginal thrush, because the infecting organism is one of the varieties of yeast. You will notice here in the unstained secretion the long mycelia with their rounded ends and

branching filaments with many new buds in the process of growth (Fig. 21). Methylene blue or Gram stain will more clearly demonstrate the organism if doubt exists as to their presence. At the same time it will give us material for examination for the gonococcus.

The treatment of vaginitis caused by the yeasts is more simple than that of *Trichomonas* vaginitis. The aniline dyes, such as gentian violet, seem to be almost specific. A few applications of a 1 per cent aqueous solution of gentian violet

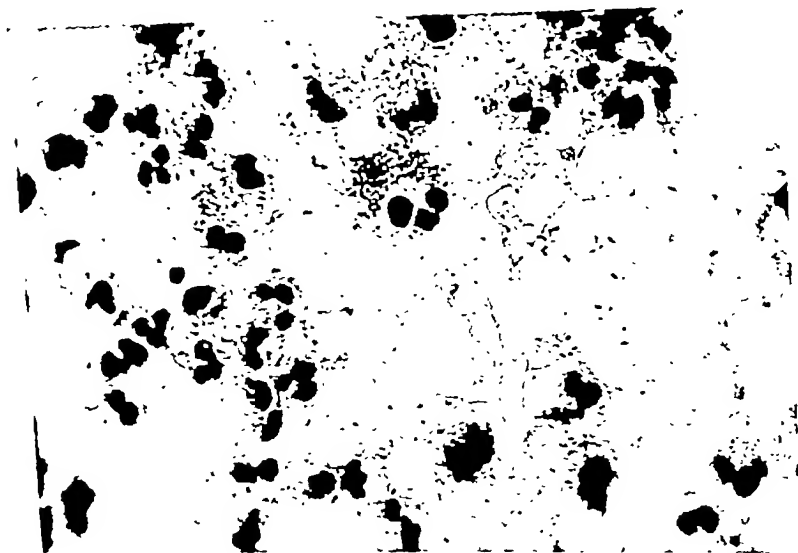


FIG. 22.—With dark-field illumination the spirochetes in this vaginal secretion could be seen in large numbers. They are probably of the type *Treponema calligyrum*.

applied to the vaginal walls and introitus is usually sufficient. However, the urine should always be examined for sugar when this infection is present. It is a very common affliction in renal and true diabetes. Cure of the vaginitis is difficult or impossible until the quantity of sugar in the urine is reduced. Daily douches containing  $\frac{1}{2}$  drachm tincture of iodine should be continued until after the next menstrual period.

This last patient, although she complains of almost identical symptoms as the other two, is afflicted with a very unusual and

interesting type of vaginitis. You will notice that the discharge is very profuse. The discharge is of the same general character as that caused by *Trichomonas* except that there are no bubbles present in it. The intense irritation about the vulva has made it difficult for the patient to walk or remain seated. Intercourse, even if attempted, has been so painful that the dyspareunia has become a major problem. In fact, dyspareunia is often the most important complaint of patients afflicted with any type of vaginitis. Any patient who complains of dyspareunia should be carefully examined for the presence of vaginal infection. The far-reaching consequences of this disability require its immediate cure. Careful examination of this secretion has failed to reveal any *Trichomonas* or yeast organisms. The stained preparations are negative for the gonococcus. Under dark-field illumination we see that it is swarming with spirochetes, probably of the strain *Treponema calligyrum* (Fig. 22). Slides prepared from this secretion and stained with Gram stain reveal the organisms in great abundance. Several strains of spirochetes besides that causing syphilis are occasionally found in the vagina. This patient's blood Wassermann and Kahn test were negative. Her symptoms will promptly disappear following a short series of vaginal insufflations with the powder that we have just described for *Trichomonas vaginalis*.



## CLINIC OF DR. NORRIS J. HECKEL

### PRESBYTERIAN HOSPITAL

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#### TRICHOMONIASIS OF THE GENITO-URINARY SYSTEM

*TRICHOMONAS vaginalis* infestation of the male genital tract is now being recognized with greater frequency, and we observe that *Trichomonas prostatitis* is no more such a rare condition. Recently, it has also been observed that *Trichomonas vaginitis* in the female may cause associated pathologic changes in the bladder and urethra.

To illustrate some of the more important findings in my studies on *Trichomonas vaginalis*, as found in the genito-urinary system, I am presenting these patients.

**Case I. *Trichomonas Prostatitis*.**—Mr. B., age fifty-one and married, is referred to me in order to determine if the prostate gland may not be the cause of recurrent attacks of *Trichomonas vaginitis* in his wife.

Except for a slight urethral discharge and occasional nocturia, this patient has no other urinary complaints.

The examination of the external genitalia reveals a very small external meatus from which a white mucoid discharge is obtained. The rectal examination shows the prostate to be slightly enlarged, especially in the left lobe with evidence of periprostatis; the right lobe is normal. The microscopic examination of the urethral smear reveals no *Trichomonas*, however, in the prostatic fluid *Trichomonas* and 2+ pus are found. The urine is normal with the exception of a few pus cells, no *Trichomonas* are present. Stained smears from the urethra and prostatic fluid reveal no intracellular nor extracellular diplococci. On exploring the urethra with diagnostic

sounds, extensive multiple strictures are found. Therefore, we can definitely say that this patient has *Trichomonas prostatitis* and strictures of the urethra.

Our technic in searching for *Trichomonas* is very simple. The prostatic fluid or urethral discharge is collected directly on a glass slide and spread not too thick. An ordinary cover slip is placed over the material and an oil immersion lens is used for observation. For office routine this procedure takes little time and, in our opinion, has been just as accurate as the hanging drop, or other more elaborate methods. One examination is not sufficient to rule out the possibility of *Trichomonas*. Searches on several different occasions should be made before a negative diagnosis is given.

In the treatment of this patient a meatotomy is first done. Then he is given prostatic massages and urethral sounds twice a week, and heat, either in the form of diathermy or an electrical heater, applied to the prostate. Urethral instillations of 20 per cent neosilvol, or irrigations of potassium permanganate, 1:3000, are used. This procedure is carried out until the prostatic fluid is free of *Trichomonas* and pus cells. In the prostate and urethra the *Trichomonas* usually disappear early, that is one or two weeks after the treatment has begun. However, the pus cells and other bacteria, usually streptococci, may be present for as long as three or four months, and it is important to continue treatment regularly until the prostate is entirely normal.

In a problem such as this, an attempt should be made to establish the primary source of the infestation if possible and thereby recognize the factors which may predispose to recurrences. In this particular patient, it is apparent since he and his wife are both infested that one may be reinfesting the other. Unquestionably, in such cases, the reinfestation is by sexual intercourse, and if either the male or female is cured, and no attempt made to search for the possibility of infestation in the other, then recurrent attacks can and do occur. Therefore, in this instance, we will advise against sexual intercourse during such time as the vaginitis, urethritis, or prostatitis is active.

In my second case, the opposite picture is present—the wife is not infested with *Trichomonas*.

**Case II. *Trichomonas* Urethritis and Prostatitis.**—This patient is forty-nine years old, married, and presents himself complaining of urethral discharge and burning of five days' duration. He fears the return of an old gonorrheal urethritis. Extramarital exposure is denied.

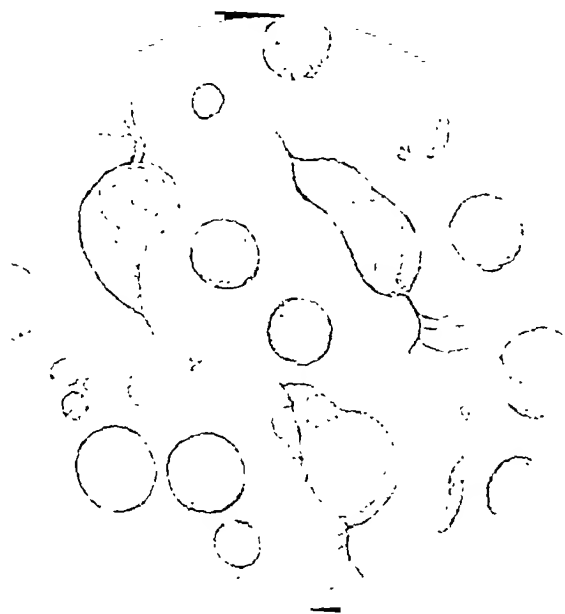


FIG. 23.—Prostatic fluid showing pus cells and *Trichomonas*.

The examination, as you see, reveals a copious amount of frothy, milky urethral discharge. The meatus is red. A small amount of the discharge is placed on a slide and examined—it is filled with *Trichomonas*. The rectal examination shows the prostate to be normal; however, the prostatic fluid contains many *Trichomonas* and pus cells (Fig. 23). Therefore, the diagnosis is an acute *Trichomonas* urethritis and prostatitis.

The treatment of this patient will be very similar to the procedure followed for the first patient, except that during

the hyperacute stage, which is usually three to six days, he will be given only sitz baths and alkalis such as bicarbonate of soda, or potassium citrate. When the acuteness of the attack subsides, then urethral instillations and prostatic massages will be carried out.

Many times it is difficult to evaluate in what way the infection occurred. In an effort to determine the origin of the infestation, the patient's wife has been examined and repeatedly the smears show no evidence of *Trichomonas*.

During the last few years, I have seen 5 cases of *Trichomonas prostatitis*. I have also had the opportunity to examine many husbands whose wives are infested with *Trichomonas* and it is surprising to find that a large number, although no *Trichomonas* can be found, do have an infected prostate, and in the culture from the prostatic fluid streptococci are usually found. According to some authors, these findings would be explained by the fact that the *Trichomonas vaginalis* itself is not pathogenic but occurs only as a secondary invader or in symbiosis. Those who hold this belief are of the opinion that the streptococcus is the pathogenic organism.

The majority of these men presented no genito-urinary symptoms, and had not an examination been made, the infection would not have been recognized. Usually the symptoms of *Trichomonas prostatitis* are the same as those of a nonspecific prostatitis; that is, a persistent urethral discharge and morning drop, associated with other various genito-urinary complaints. The condition, however, may start as an acute urethritis in which the discharge has a frothy, bubbly appearance, burning and frequency of urination, and an itching or smarting of the urethra may be present. I have not as yet seen a patient with a *Trichomonas urethritis*, who did not also have an associated prostatitis. In the rectal examination, the prostate may be entirely normal in size, shape and consistency, or there may be areas of hardness and infiltration. It is never tender nor swollen as in acute gonorrheal prostatitis. In venereal infections those having nonspecific urethritis and prostatitis are not a small number, and if more careful bacterio-

logical examinations are made, I am sure that in a larger percentage of the cases *Trichomonas* infestation will be found.

My third case is that of a woman with recurrent *Trichomonas* vaginitis in whom the urinary symptoms are pronounced.

**Case III. Recurrent *Trichomonas* Vaginitis.**—Mrs. H., aged forty, has been treated elsewhere during the past six months for recurrent attacks of *Trichomonas* vaginitis. These attacks have been accompanied by aggravating urinary symptoms of frequency every two or three hours, nocturia four or five times, with burning and dysuria. Here I should like to stress the importance of obtaining a careful and accurate history. Because of the severe vaginal symptoms of leukorrhea, scalding, and dyspareunia which frequently occur in these patients, definite questions must be asked in order to elicit information concerning the urinary complaints.

This patient has had a complete and thorough examination of the gastro-intestinal tract, teeth, tonsils, Bartholin and Skene glands as a possible focus for the recurrent vaginitis attacks, and all are negative. In the bacteriological study of the cultures taken from the vagina and cervix, streptococci have been found. I might also add that the same strain of streptococci has been cultured from the prostatic fluid of her husband, who, although no *Trichomonas* have been found, does have an infected prostate.

Because of the patient's urinary symptoms a cysto-urethroscopic examination is done. The urine, as you see, is clear and sparkling and a specimen is collected for bacteriological study. Your attention is called to the normal capacity of the bladder. This is an important observation to be used in the differential diagnosis from elusive ulcer in which the bladder capacity is greatly diminished.

The pathologic changes are seen on the base of the bladder in the region of, and anterior to the trigone. In some cases these changes may extend beyond the trigone and involve both the ureteral orifices; in others may be limited to the internal urethral sphincter. Observe the raised, granular, fluffy and

crepelike appearance of the bladder mucosa. It is a dull, pearly gray, and resembles somewhat the appearance of leukoplakia. The borders of this area can be sharply outlined from the normal mucous membrane. Notice the small petechial hemorrhages around this region which appear very similar to the surface of a strawberry. These changes look similar to those found in the vaginal vault of many patients with *Trichomonas vaginitis*. As the cysto-urethroscope is withdrawn into the urethra, note the marked edema around the internal urethral orifice, and the pronounced changes similar to those in the bladder.

This cystoscopic picture is seen quite frequently in *Trichomonas vaginitis* and I feel that in patients who complain of lower urinary symptoms, if these findings are observed, a careful search of the vagina should be made for *Trichomonas*.

In summarizing the condition of this patient, we find two possibilities for the recurrent attacks of the vaginitis. First, although *Trichomonas* were not found in the prostatic fluid of the husband, he did have an infected prostate and the same strain of streptococci was isolated from the prostate as was found in the vagina and cervix of the wife. He, therefore, may be the cause of his wife's recurrent attacks. Second, the cause may be found in the pathology of the urethra and the bladder. I have seen patients in whom, after the associated pathology in the urethra and bladder was cleared up, there have been no more recurrent attacks.

In the treatment of this patient until the acute condition subsides, we will follow this procedure: she will be given sitz baths, 2 or 3 daily, and internal medication of oil of sandalwood 5 minims, t.i.d., and alkalis such as sodium acetate 20 grains, or bicarbonate of soda, four times daily. Then the bladder is irrigated with an oxidizing agent such as 1:3000 solution of potassium permanganate followed by instillation of 2 to 3 ounces of 15 per cent neosilvol, or 20 per cent argyrol, twice a week. At the same time, topical applications to the urethra of 2 per cent silver nitrate solution, or  $\frac{1}{2}$  of 1 per cent zinc sulphate are used. If urethral pockets or other per-

sistent ducts in and about the urethra are present, it may be necessary to fulgurate them. The second part of the treatment will be directed to the husband and the prostatitis treated as previously outlined.

#### CONCLUSIONS

1. Each of the three patients presented to you illustrates an interesting phase of the *Trichomonas vaginalis* infestation.

2. The first is an example of the infestation probably through sexual intercourse, since both the husband and wife are infested.

3. The second patient illustrates an infested prostate and urethra, but no infestation in the wife. Furthermore, the history and examination of husband and wife in this instance give no solution as to the source of the infestation.

4. In the third case, which is that of recurrent vaginitis with urinary symptoms, we find first that while *Trichomonas* were not found in the prostate gland of the husband, a prostatitis was present, offering a possibility for the cause of the recurrent attacks of vaginitis. Second, the associated changes in the urethra and bladder indicate that the recurrences may be caused by these findings.

5. It cannot be too strongly emphasized that repeated examinations of the urethral discharge or the prostatic fluid must be made in many instances in order to find the *Trichomonas*.

6. In patients with so-called "nonspecific" urethritis and prostatitis a more careful examination will reveal a higher percentage of *Trichomonas* infestations.





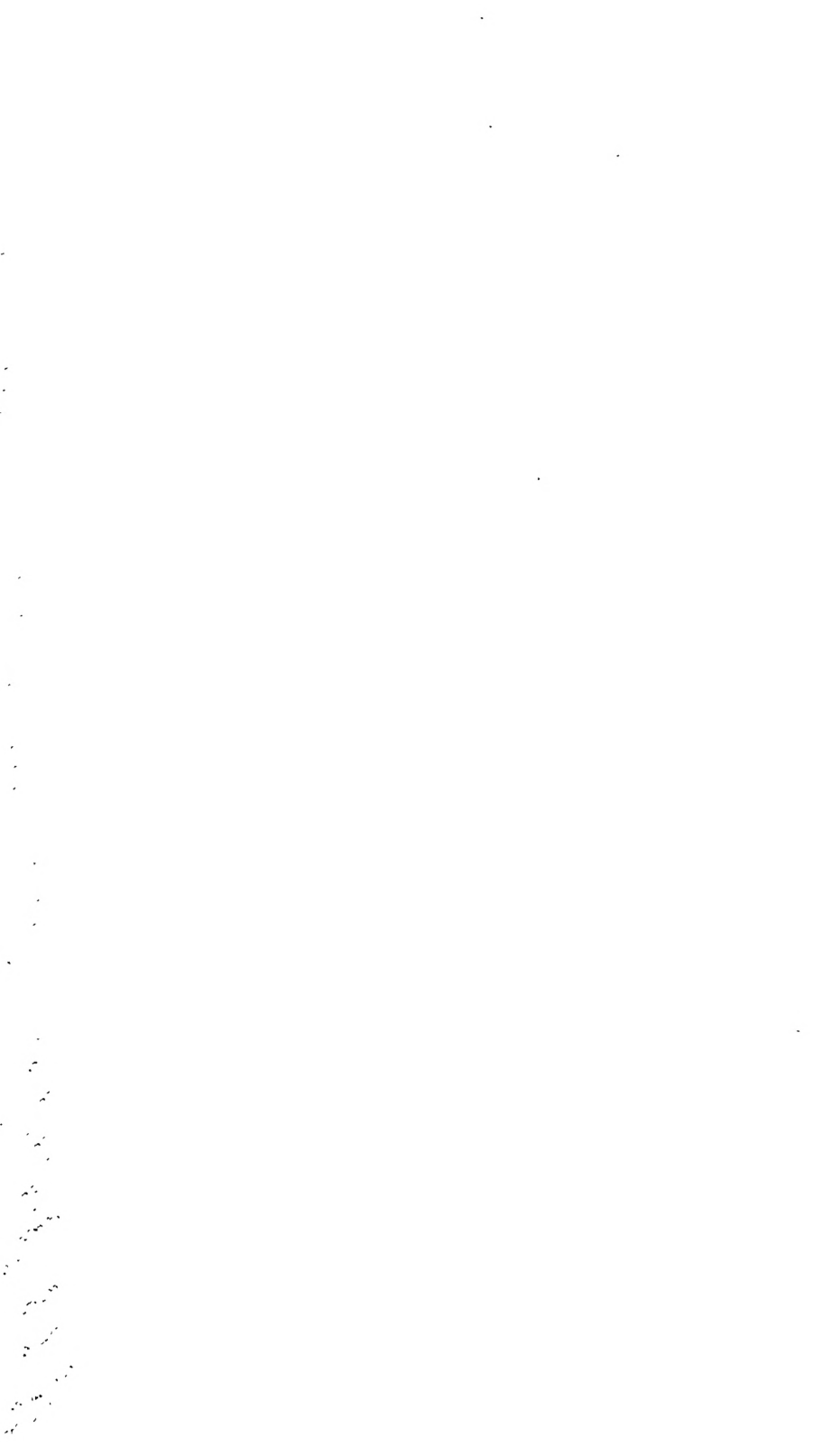
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# THE MEDICAL CLINICS OF NORTH AMERICA

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## SYMPOSIUM ON BLOOD DYSCRASIAS

The following clinics are included in this Symposium:

William P. Murphy: *PERNICIOUS ANEMIA.*

Francis T. Hunter: *THE LEUKEMIAS: THEIR DIAGNOSIS, PROGNOSIS AND TREATMENT.*

Henry Jackson, Jr.: *NOTES ON THE TREATMENT AND PROGNOSIS OF HODGKIN'S DISEASE AND ALLIED DISORDERS.*

Roger I. Lee: *A CASE OF POLYCYTHEMIA VERA OR ERYTHREMIA.*

R. Cannon Eley: *HEMOPHILIA.*

Clark W. Heath: *IRON DEFICIENCY IN GIRLS: CHLOROSIS.*

Louis K. Diamond: *CONGENITAL HEMOLYTIC ANEMIA IN INFANCY AND CHILDHOOD.*



## CLINIC OF DR. WILLIAM P. MURPHY

FROM THE MEDICAL CLINIC OF THE PETER BENT BRIGHAM  
HOSPITAL

---

### PERNICIOUS ANEMIA

#### DIAGNOSIS

In October, 1931, Mr. J. D., a sixty-four-year-old electric car motorman, walked into the out-patient department for an examination. No, he had no complaints; he had noticed only slight shortness of breath while walking to work, but the boys at the shop had told him that he was losing his usual ruddy complexion. Except for a slight pallor, physical examination failed to reveal any important indication of the presence of an illness. His color was fair, but in a good light the sclerae appeared to be slightly icteric. The examining physician, however, was not satisfied to do the customary routine examination of the urine and dismiss his patient with a tonic, a word of encouragement and a diagnosis of psychasthenia. He requested a blood count. This revealed a red blood cell level of 1,000,000 cells per cubic millimeter! Furthermore an examination of the stained blood film revealed a preponderance of large cells with many very large and oval-shaped forms and a fair number of pear-shaped and tailed forms.

Here then, reasoned the careful examining physician, is a man who walked into the hospital after his customary early morning run on his car with a red blood cell count of one million—certainly not a hypochromic type of anemia—for no one with this type of anemia and such a blood count would be out of bed. Then, too, there was evidence of a macrocytic anemia with pear-shaped cells and evident icterus of the sclerae. Even in the absence of a history of sore tongue or glossitis and disturbances which result from neural damage, the examiner felt justified in making a diagnosis of pernicious anemia and convinced the patient that his condition warranted hospitalization for treatment.

In the hospital the examiner's diagnosis was further con-

firmed by means of a fractional gastric analysis which failed to show free hydrochloric acid in any specimen even after the injection of histamine and also by the observation of the prompt and striking increase and decrease of the reticulocytes of the blood during a period of ten days following the intramuscular injection of a highly potent solution of liver extract. This patient with continued intramuscular therapy has been maintained in a normal state of health with a normal red blood cell level (5,000,000 or more cells) and has been able for more than five years to continue at work.

Therefore, because the examining physician was aware of the importance of an examination of the blood as well as the urine, a puzzling problem was solved and the development of complications which might have occurred through delay in treatment was avoided.

With the appearance in a patient of the characteristic clinical signs and symptoms a diagnosis of pernicious anemia may be made readily and with confidence. Laboratory studies of the blood may then be utilized merely to confirm the diagnosis and to indicate the severity of the anemia or to demonstrate the course of improvement of the blood following treatment. Unfortunately, however, cases presenting a typical picture of this disease represent only a portion of those who will present themselves for diagnosis. If one is to avoid overlooking those cases which do not present the characteristic clinical picture of pernicious anemia, it is important to study the blood routinely. The average physician equips his office so that routine examinations of specimens of urine may be made; but how many are equipped to make even the simplest blood examination by an accurate method?

The importance of a satisfactory examination of the blood is illustrated by the case of one of my patients, Miss R. O., a high school teacher in one of our large cities, who had consulted 5 physicians because of poor health. She was advised by the last one consulted to obtain a year's leave of absence and to travel for a much-needed rest. Her difficulties steadily increased during the trip until finally she collapsed in a small

town in India where the only physician for miles around made a diagnosis of pernicious anemia and started liver therapy. None of the first 5 physicians consulted had made any sort of examination of her blood.

Information sufficient to establish the presence of anemia will be obtained by a determination of the hemoglobin level. This may be done with reasonable accuracy by the use of a standardized Sahli apparatus which is inexpensive and also simple to use. Further indication of anemia may be obtained by even a brief study of a stained film of the blood. In order then to determine the cause for, or type of, anemia present, careful questioning as to loss of blood from hemorrhoids or, in the case of female patients, from the genital tract is essential and the necessity for a guaiac test of the feces to detect hemorrhage from the gastro-intestinal tract cannot be over-emphasized.

On the other hand, demonstrable anemia may not be present as the earliest evidence of pernicious anemia. Consequently it is important to bear in mind constantly that a rather persistent sore tongue or mouth occurring in a patient with no obvious roughening or abnormality of the teeth to account for the irritation, which has not been controlled by the customary local applications, may be the first evidence of this disease.

The typical tongue of this disease, rarely simulated by that occurring in any other anemic state, with the possible exception of sprue, either tropical or nontropical, is clean and almost never coated. Rarely are there localized ulcerations as in canker, but to the contrary the sides or even portions of, or the entire, surface may appear inflamed, with a beefy-red color and may often be distinctly glossy. The pale, smooth tongue may at times be present but is more likely to be observed in hypochromic anemia. The glossy, inflamed areas, wherever present, are highly susceptible to irritation. Hot or "sharp-tasting" foods, salt and the like may produce such irritation that the food intake becomes limited. Patients using dentures find difficulty in wearing them, consequently the

food intake is decreased. The sufferer tries one set of dentures after another hoping each time to discover some fault in the previous ones which would cause the irritation of the mouth. These changes in the mucous membranes may precede by months, or even a year or two, severe anemia or other evidences of the disease, and may persist constantly or intermittently for weeks, months or years, failing to respond considerably or permanently to any treatment other than that specific for pernicious anemia.

Although the sore mouth or glossitis is perhaps most frequently observed as the forerunner of the disease, disturbances resulting from neural damage are not infrequently present as the primary evidence of trouble and may occur, though rarely, in the absence of obvious blood changes. Because of the variations in neural disturbances and the bizarre or even "atypical" picture occasionally encountered, one must constantly be on the alert to recognize them as they may be symptomatic of pernicious anemia. Let us realize in the first place that their permanency rather than their extent is important. In pernicious anemia transient disturbances rarely, if ever, occur. Although numbness or tingling or both may involve only a hand or even two fingers of one or both hands, these will be persistently noted throughout the day and the waking hours of the night, whereas transient disturbances of a similar sort may be observed by the patient with hypochromic anemia or without anemia.

Numbness, tingling or a combination of the two are perhaps the most commonly described neural symptoms, and as suggested above, they may be limited in distribution or may involve both hands, both feet, and even extend well up onto the abdomen and back. As this condition becomes more marked, the sense of touch may be impaired. Not infrequently the patient complains of an inability to feel the floor with the feet while standing, or there may be a sensation as of walking on a thick carpet, or, if paresthesias are present, of walking on eggs or pointed stones. In one patient, a carpenter, the numbness of the hands became so intense that he was unable



to feel the handle of a hammer in his hand. As he glanced at the head of the nail to strike it, his grip on the hammer would be lost, and he would find it on the floor.

Paresthesia of the hands may become so severe that it is practically impossible to use the fingers unless protected. For this reason one patient constantly wore gloves. A housewife became practically an invalid owing to the excruciating pain induced even by touching her knife and fork at meal time.

Other common complaints are those of tightness and coldness of the extremities. Patients often describe these sensations by saying that they feel as though there were tight bandages wrapped about the legs. One patient said he felt as though he were standing in a cold stream in hip boots; another said that her hands felt as though they were in cold water with tight rubber gloves on.

The locomotor difficulties are more readily understood by the examining physician than are the neural disturbances which produce only subjective complaints. Locomotion may be altered at times because of the weakness resulting from severe anemia or because of the severe numbness previously described. With involvement of the lateral columns of the spinal cord, however, a more severe locomotor difficulty will be present. Either a spastic or flaccid paralysis may occur. Spastic difficulties are most common and occasionally are of such a nature that the knees may be permanently flexed, or the thighs may be tightly drawn together, or crossed. The reflexes are typically altered depending upon the type of involvement, but alterations in skin, tactile, pain and temperature sense rarely occur. In the presence of marked locomotor disturbance the ability to recognize tuning fork vibration over the tibiae is almost always lacking.

Jaundice is rarely present early in the course of the disease but may be observed in untreated patients with red blood cell levels of about 2,000,000 or less. The presence of jaundice produces the rather typical lemon or grapefruit colored pallor with the yellow sclerae which should at least suggest a diagnosis of pernicious anemia. At one time this jaundice was

thought to have been caused by unusual hemolysis of the red blood cells, but in view of our present knowledge of the disease it seems more logical to relate this, at least in part, to decreased utilization of the bile pigments.

### FAMILIAL INCIDENCE

The occurrence of pernicious anemia in two or more members of the same family group has often been noted, and such a tendency has been notable in my own series of patients. I wish to present briefly a few interesting examples of this.

Miss D. R., a school teacher, had developed the disease at the age of forty and was started on parenteral liver treatment, which has been continued faithfully for nearly five years with complete control of all symptoms. Several years after the onset of her illness she brought in her mother, then seventy-five years of age, for examination because of the occurrence of symptoms similar to those which had originally led her to seek medical advice. A diagnosis of pernicious anemia was obvious also in the case of the mother and now both receive treatment.

Miss N. S., a fifty-nine-year-old seamstress, who had been treated in the blood clinic for several years, brought in her fifty-six-year-old sister for examination because of symptoms similar to her own original ones, and again a diagnosis of pernicious anemia was readily made. Both these sisters have now continued parenteral treatment in the clinic for five years with satisfactory control of those disturbances primarily related to the anemic state. It is interesting to note, however, that both these sisters also have hypertension of moderate degree.

A third case of rather noteworthy interest is that of Mrs. F S, who is able to trace the occurrence of pernicious anemia through five generations. A cousin (the daughter of the patient's mother's sister) is known to have had pernicious anemia, and this disease also exists in a distant relative who is descended from a common ancestor eight generations back in the relative's family and nine generations from Mrs. S.

One point of particular interest in the case of Mrs F S is the certainty of diagnosis through so many generations. This is because of the fact that the same symptoms, soreness of tongue and mouth, and extreme hyperesthesia of the fingers and hands, had been recorded during the course of a fatal (in all except the last case) illness, associated with anemia, in each patient. Mrs F S, now seventy years of age, is one of five children, three of whom have had pernicious anemia. She has three adult children, none of whom has shown signs of this disease. Two sons although married for several years have no children; the wife of one had a child by a former marriage. The daughter, the patient's third child, had one child after being married for nine years.

There has been a steady trend toward fewer and fewer children with each generation so that the family is steadily decreasing in number. Each of the victims of the disease, except those in this generation who have had the advantage of liver therapy, has died before the age of fifty.

### TREATMENT

The next case which I wish to present is that of Miss B. S., a fifty-two-year-old cook, who first came to the blood clinic in April of 1936, with a normal red blood cell level (5,000,000 cells per cubic millimeter) and apparently in splendid health except for evidence of moderate locomotor difficulty and a complaint of persistent numbness of the hands, feet and legs up as far as the knees. Approximately eight months previously a diagnosis of pernicious anemia had been made while she was in another hospital. The chief complaint at that time, other than some degree of anemia, the severity of which she does not know, was extreme locomotor difficulty so that she could neither stand nor walk without aid.

While in the hospital treatment by means of intramuscular injections of liver extract was started. This consisted of injections of 5 cc. of a solution of liver extract of low concentration twice a day for about two months, after which time she received a similar injection once a day until she entered our blood clinic eight months later. During this time the injections were given by a district nurse whose daily charge was fifty cents.

This case illustrated two important points. In the first place we must all agree that an adequate amount of liver substance was administered to produce and maintain a normal red blood cell level (5,000,000 or more red blood cells per cubic millimeter). In the second place as was to be expected from the use of a sufficient supply of liver substance to maintain the blood at that level regardless of the method of administration, an improvement in locomotor and other disturbances caused by neural damage occurred, and we find the patient returned to a rather satisfactory state of health.

But what has it cost this patient, dependent upon her own earnings for a livelihood, to obtain this amount of improvement? The daily cost of liver extract (on the basis of 1 injection daily of 5 cc.) was 62½ cents. In addition to this she paid 50 cents for each injection. Thus her actual expense for three hundred and sixty-five days would be \$410.63! This amount does not take into consideration the original cost of hospitalization, physician's fees, nor her loss of earning power

during this time, as it was practically impossible for her to work and receive the daily injections.

What a contrast to her experience is that of the patient in our blood clinic who finally convinced her of the needlessness of such treatment and persuaded her to arrange for subsequent treatment in the clinic. His case is as follows:

Mr. W. P., a war veteran, forty-six years of age, who had essentially comparable neural disturbance, except that locomotion was less strikingly affected, has been under treatment for four years,, receiving injections of 3 cc. of a concentrated solution of liver extract at intervals of slightly more than four weeks. In order to maintain his blood at a level constantly above 5,000,000 cells per cubic millimeter and to bring about almost complete alleviation of the neural disturbances, he has received not over 12 injections per year at \$1.20 each or less than \$15.00 a year. Even allowing for the extra cost of a nurse, or even of a physician to give the injection, the expense is still minimal.

It is not logical of course to contrast the treatment received by two individual patients, for each patient's needs vary, depending upon several circumstances. As I have previously reported, however, the average patient in our blood clinic requires only 1 injection of either 1 or 3 cc. of concentrated solution of extract every three or four weeks in order to maintain the blood in a normal state and to produce an optimal state of health. Were the patient to receive the maximal amount of treatment (either 1 or 3 cc. per week), the expense of treatment would be relatively small in contrast to that of daily injections. The difference in the inconvenience to the patient is considerable.

Are we not as physicians, to some extent at least, conservators of our patients' money? Should we not utilize those available means of treatment which will best serve the needs of the patient and which will accomplish the desired result with a minimum of expense and inconvenience to the patient? The surgeon no longer sprays the operating room with carbolic acid in order to avoid wound infection, and the cardiologist is no longer content to treat his patient with hit-or-miss dosages of digitalis of low or unknown potency. Is not the patient with an anemia readily controlled by the anti-

anemia factor contained in liver entitled to treatment by means of the most modern therapeutic measures available?

Although the introduction of a liver extract so prepared as to be of practical value for parenteral injection was heralded as a definite improvement over the use of liver substance perorally, the development of the means of preparing more concentrated extracts for intramuscular injection without appreciable loss of potency and without those irritating substances so characteristic of the less carefully refined material is, particularly for the patient, a most important step in advance. It seemed almost miraculous to be able to produce the striking results observed following the use of a liver extract so concentrated that 3 cc.\* contained the active substance from 100 Gm. of liver. It seems even more remarkable, however, to realize that even further concentration has been accomplished so that one third of this volume or 1 cc.\* contains the active principle from 100 Gm. of liver without loss of potency. The results of the use of this most highly concentrated extract after one and one-half years of experience with it have been reported elsewhere by the author<sup>1</sup> but a brief review of its use in one patient may suffice to indicate the advantages of this modern means of therapy.

Miss F. C., a twenty-seven-year-old salesgirl, entered the hospital on April 9, 1935, with a red blood cell count of 1,000,000 per cubic millimeter. An injection of 4 vials or 4 cc. of a highly concentrated liver extract (Lederle) derived from 400 Gm. of liver, was given the following evening, followed on the morning of the fifth day by a reticulocyte peak of 32.8 per cent. By April 23, the red blood cell count had risen to 3,170,000, a daily increase of 170,000. On April 27 another injection of 1 vial or 1 cc. was given. By May 22, 1935, the red blood cell count had reached a level of 4,550,000 since which time (up to September 29, 1936) she has received 21 injections, each 1 vial or 1 cc., of highly concentrated liver extract intramuscularly.

This patient has therefore received 26 cc. or 26 vials of extract during a period of five hundred and thirty-seven days during which time her red blood cell level has been returned to normal and maintained at an average level of 5,430,000

\* N N R Lederle Laboratories, Inc., Pearl River, N. Y.

cells per cubic millimeter. She has remained steadily at work since May, 1935, returning to the clinic for an injection of 1 cc. of liver extract only at intervals averaging slightly over three weeks. A blood examination has been made at practically each visit in order to insure maintenance of the blood at a normal level.

The need for regulation of the amount of liver substance necessary for the adequate treatment of each patient according to his own requirement has been mentioned. It is difficult to state arbitrarily how frequently a patient's blood should be examined in order to insure its maintenance at a proper level, for this again varies according to certain factors present. Immediately following the reticulocyte rise precipitated by initial treatment, it may be well to examine the blood at each weekly interval that the patient returns for an injection, until a normal or 5,000,000 level has been reached. Examinations thereafter may be made at intervals of one, two or three months, depending upon the state of the blood. If it remains well up to normal, the less frequent intervals may be sufficient. If there is a lag or tendency for the blood level to drop, more frequent examinations will be needed.

The occurrence of an infection or other complication usually is an indication for examination at more frequent intervals than might otherwise be necessary. After the amount of treatment necessary to maintain a normal blood level has been established by treatment for a year or more, examinations of the blood levels may be made only once during four to six months, providing no complication occurs during this time. In no case is it sufficient to test only the hemoglobin level during the course of maintenance treatment because in pernicious anemia this may not satisfactorily indicate the condition of the blood. It is best to follow both hemoglobin and red blood cell levels and certainly the latter. If the level of the red blood cells is not compatible with the clinical state of the patient, an examination of the stained blood film will allow one to decide whether or not the technician has counted the cells correctly.

This is illustrated by the case of a patient, Mr. A. M., who was referred to me for consultation. Mr. A. M. had begun treatment at a time when there was evidence of neural damage which resulted in moderate locomotor difficulty. This condition improved with treatment, but at the end of a year there was again evidence of progression in spite of the fact that sufficient liver was being taken to maintain a count reported to be around 5,000,000. In my laboratory, however, the red blood cell level was found to be only 3,500,000. Which count was correct? An examination of the stained film showed the presence of many oval macrocytes with a tendency to increased size of the cells (confirmed by determination of the individual cell volume) and also many pear-shaped cells, a picture hardly compatible with a normal count. More intensive treatment was instituted, and as the blood returned to normal the neural disturbances again decreased.

The red blood cells, in the presence of a normal level even in a patient with pernicious anemia, should be normal both as to their appearance in a stained film and as to individual cell volume as determined by the hematocrit method.

#### PROGNOSIS

A question frequently asked by one's patient is, "How long must I continue to take liver in some form in order to remain well?" The answer is, that in the light of our present knowledge of the disease, treatment should be continued throughout life. This answer usually provokes the second question, "How long may I expect to live providing treatment is continued?" The answer to this seems to be equally well established on the basis of our experience with treatment during a period of over ten years. In so far as the pernicious anemia is concerned, one should expect to live at least as long as the average individual of his own age. In other words a satisfactorily treated patient should not die from circumstances associated with pernicious anemia but rather from some totally independent illness. Of course it must be realized that many complicating illnesses are of such a nature that it may become increasingly difficult or even impossible entirely to control the pernicious anemia so that the terminal illness may include difficulties related to that disease.

The following cases are illustrative of typical experiences in respect to life expectancy.

Mrs. R. G., a housewife, was first diagnosed as having pernicious anemia in the fall of 1921, at the age of forty-five. Transfusions were effective in maintaining life through three relapses until the early spring of 1925, when liver treatment was begun. Treatment has been continued rather satisfactorily up to the present time and the patient remains in excellent health at the age of sixty-one. According to figures published by the Metropolitan Life Insurance Company<sup>2</sup> the expectation of life at birth from 1911 to 1935, the last report available, was fifty-nine and nineteen one-hundredths years. Their figures also show an expectation of life of twenty-four years for a white female forty-five years of age in 1921. One may therefore expect this patient to live to be sixty-nine years of age. The prognosis is excellent.

Mrs. J. G., a widow, has been observed in the out-patient clinic from time to time because of various ailments since 1915. Up until the spring of 1926, when a diagnosis of pernicious anemia was made at the age of sixty-five, none of these was of such a nature as to suggest this diagnosis. Since 1926, when liver treatment was started, hypertension gradually developed during the first two or three years and four years ago when the patient was seventy-one years of age diabetes mellitus appeared acutely. From the time the diagnosis was made until the spring of 1931, treatment consisted either of whole cooked liver or peroral extract. Since that time intramuscular injections have been used. In spite of the complications noted, this patient at the age of seventy-five remains in a fair state of health with a normal red blood cell count. Again using the Metropolitan Life Insurance Company's<sup>2</sup> expectation of life figures one might expect this patient to live eleven and seventy-five one-hundredths years after the age of sixty-five or approximately to the age of seventy-seven. Certainly one could hardly expect a longer life for an individual with hypertension and diabetes alone.

By far the greater number of persons show evidence of pernicious anemia between the ages of fifty and seventy years than at any other age. The exceptions to this rule, however, are interesting. One patient now being followed in the clinic at the age of eighty-five had nothing in her history or symptomatology to suggest a diagnosis of pernicious anemia until after her eightieth birthday. She is still in excellent health. In several instances the onset of the illness occurred before the age of twenty. I have just had occasion to study a girl, thirteen years of age, who presents a typical blood picture of pernicious anemia, has complained of intermittent, fairly long intervals of sore tongue, has achlorhydria even after the use of histamine, and whose blood response to intramuscular injections of liver extract has been excellent. A negative family history, absence of enlargement of the spleen and



normal fragility of the red blood cells make a diagnosis of hemolytic ictero-anemia highly improbable.

In view of the accumulating number of patients with experiences similar to the typical ones presented, it is obvious that the life span of the pernicious anemia patient may be lengthened by at least ten years (except of course in the older age groups in which the life expectancy of the normal is less), and by continuance of careful control and advice, the life span need not be limited by disturbances directly credited to pernicious anemia.

Although the prognosis, so far as expectation of life is concerned, in a patient with uncomplicated pernicious anemia, may be considered to be excellent, maintenance in a state of economic efficiency for the duration of life is to be considered of almost, if not quite, equal importance. Perhaps the greatest difficulty encountered in this respect is the occurrence of disability resulting from sclerosis of the spinal cord. According to data recently reported by the author<sup>3</sup> concerning the complications occurring in 440 cases, 270, or 61 per cent, presented signs or symptoms indicating some degree of sclerosis. Only 151 had evidence of lateral column involvement, while 42 had evidences of severe locomotor difficulty. Little need be said here in regard to the value of liver therapy in preventing and improving these disturbances inasmuch as this subject has been discussed in many reports. An excellent review of the literature on this subject has recently been presented by Schaller and Newman.<sup>4</sup>

From the evidence now available, certain facts concerning the disturbances associated with neural sclerosis seem to be well established, and it may be desirable to mention them here.

In order to prevent progression of these disturbances to such an extent that the patient will be permanently handicapped in respect to locomotion, it is important to start intensive liver treatment early and to continue an adequate dosage to maintain the red blood cell count at a high normal level. If this is not done and destruction of the nerves is

allowed to continue for a period of months or years, considerable improvement is not to be expected.

If the blood is maintained in a normal state (5,000,000 or more cells per cubic millimeter), disturbances resulting from neural sclerosis do not appear. If they are present when treatment is started, they do not progress, and improvement occurs. The amount of improvement will depend upon several circumstances but primarily upon the amount of nerve damage present at the time adequate therapy is instituted, which in turn usually is dependent upon the length of time that elapses before satisfactory treatment is established.

Satisfactory results will be obtained with maintenance of the blood in a normal state regardless of the method of administration of liver therapy. As this is most readily accomplished by means of parenteral therapy, this method is considered the one of choice.

The institution of exercises designed to retrain the muscles paralyzed and to improve the balance of the patient may favor more rapid and complete recovery of the function of locomotion.

So many excellent, almost miraculous, results have been observed in patients exhibiting marked locomotor difficulties that it is very difficult to choose one or two of the most interesting to present. On the other hand, the failures have been so unusual that the following case may best illustrate the points emphasized above.

Mr. J. O., a forty-five-year-old war veteran, presented himself for treatment with a red blood cell count of 900,000. He was unable to walk or to stand without aid. This patient had been treated in a veterans' hospital during a two-year period, usually with a moderate dose of a council-accepted liver powder. Locomotor difficulties had been present during this period, and in spite of some liver therapy the red blood cell level had not only remained subnormal but also had actually dropped to the low level recorded. Of course the result was progression of the cord difficulty to the worst possible state. With intensive treatment by means of intramuscular injections it has been possible to maintain the blood in a satisfactory state, and locomotion has been slightly improved. Further improvement probably cannot be obtained because of the degree of damage present. As a result of inadequate therapy this patient will be unable to become an economically efficient member of society. Had he re-

ceived earlier the benefit of adequate treatment, so readily available, this tragedy need not have occurred.

The cases of the 2 following patients illustrate the bright side of the problem; in the second instance even in spite of rather prolonged inadequate therapy.

Mrs. A. D., a thirty-eight-year-old housewife, began treatment in January of 1932 with intramuscular injections of a concentrated solution of liver extract. At this time she was confined to bed and was unable to walk because of locomotor disturbances resulting from spinal cord sclerosis. The red blood cell level was then 2,000,000 cells per cubic millimeter, hardly low enough to increase the locomotor difficulty because of weakness. As treatment brought the blood levels back to normal and exercises designed to retrain the paralyzed muscles were carried on, locomotion improved. At first it was necessary to lift her into and out of an automobile and to a wheelchair in order to get her to the clinic for treatment. Within three months she was able to walk alone, and today she is a picture of health and has no evidence of locomotor disturbance.

The diagnosis in this patient was made and intensive treatment begun early in the course of the disease before the spinal cord damage had advanced to an irreparable stage. Under such circumstances even those evidences of pernicious anemia, which may prove to be serious handicaps to economic efficiency, are readily controlled.

. In January of 1932, Miss R. O., previously mentioned, a forty-five-year-old school teacher, whose illness began rather insidiously with frequently recurring attacks of diarrhea over a period of several years, followed by a tendency to tire easily and a sore tongue and mouth, presented herself for treatment.

During the early part of her illness several physicians, who were consulted, failed to make a diagnosis, but on the advice of one of them, a year's leave of absence was taken to travel and rest. While traveling fatigue became more and more intense, the diarrhea increased, and evidence of cord sclerosis appeared making further travel impossible. She then consulted a medical missionary, the only physician in the vicinity of a small town in India, who made a diagnosis of pernicious anemia and advised liver therapy. Her condition improved sufficiently to allow her to continue her journey. During this time some evidence of locomotor difficulty had appeared, but while at a large "clinic" in the West, it became acutely worse following an "adjustment" of the spine, which was to have "cured" her illness. At this "clinic" a diagnosis of psychasthenia was made, and the possibility of sprue was considered. The liver treatment was stopped. During the ensuing year numerous physicians consulted made varying diagnoses and gave conflicting advice. Through it

all, however, liver treatment was continued irregularly, but it was not of sufficient intensity to bring about any considerable improvement.

She had presented herself for treatment, however, after a period of rather intensive liver therapy, and therefore, her blood was in a fairly satisfactory state although the attacks of diarrhea persisted unless controlled by opiates, and she was unable either to stand or walk unless supported. Intensive intramuscular liver therapy and exercises for the purpose of retraining the paralyzed muscles and improving the balance were started. In spite of the long-standing and progressive locomotor difficulty this patient has been able, after approximately two years of incapacity, to return to her teaching position in an excellent state of health and without sufficient locomotor difficulty to be recognizable by one not familiar with her condition.

Needless to say such a splendid improvement has not been obtained by a careless, haphazard observance of the treatment instituted, but it is the result of the most meticulous attention to all the details of treatment, especially those necessary for maintenance of the blood in a perfectly normal state, and an indomitable will to return to a normal state of health and to the status of a self-supporting member of society.

What a pleasure it is to supervise the treatment of a patient whose cooperation and desire to recover a normal state of health has been so enthusiastic! The majority of patients with pernicious anemia will be found willing and anxious to cooperate. With sympathetic encouragement and thoughtfully considered advice in respect to the details of treatment of the various problems as they arise, results equally satisfactory may be obtained in virtually all instances.

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## CLINIC OF DR. FRANCIS T. HUNTER

IN CONJUNCTION WITH THE X-RAY DEPARTMENT OF THE  
MASSACHUSETTS GENERAL HOSPITAL

### THE LEUKEMIAS: THEIR DIAGNOSIS, PROGNOSIS AND TREATMENT

In sketching for you the diagnosis, prognosis, and treatment of the leukemias, I must ask you to consider not only chronic myelogenous and chronic lymphatic leukemia but also those rarer forms of the same group of diseases, *aleukemic leukemia* (both myelogenous and lymphatic), *pseudoleukemia*, and *acute leukemia*. Since our allotted time is so short, it occurred to me that I might more clearly convey to you the usual course and clinical picture encountered in these conditions by presenting imaginary rather than real patients. I have, therefore, telescoped the more common events and findings into single cases and offer them as samples of what one might expect to meet with in a general practice.

#### CHRONIC MYELOGENOUS LEUKEMIA

Let us, then, consider Mr. A., a man in his late thirties, who comes to us complaining of fatigue and of the presence of a mass in the abdomen. Giving no definite date of onset of his symptoms, he tells us that for the past six to eight months he has felt somewhat unwell, and that three months ago he noted a mass in the left upper quadrant of the abdomen. Although not painful, a sense of pressure and a dull aching in the region of the tumor first drew his attention to it. On closer questioning he admits some loss of weight, increased perspiration, and vague gastric distress. He stoutly denies excessive bleeding or abnormal bruising, and adds that if it

had not been for the insistence of his wife, he would not have consulted a doctor.

When we examine him, we find little to attract our attention excepting a slight pallor, a warm skin, and an enlarged spleen; the latter, on careful palpation, is observed to extend to the level of the iliac crest. On examination of his blood, however, we discover a slight anemia (3,900,000 red corpuscles per cubic millimeter), and a leukocytosis of 150,000 per cubic millimeter. A study of the white cells in the stained smear shows them to consist almost entirely of elements of the polymorphonuclear series at various stages of maturation. The predominant cell is the myelocyte, but we find, in addition, many immature polymorphonuclears, a few myeloblasts, and an occasional nucleated red cell. The red cells themselves show only slight changes in size and shape and seem to be fairly well filled with hemoglobin. We decide that the platelets are somewhat increased in number. Moreover, on two consecutive determinations the basal metabolism rate is elevated above plus 40 per cent.

As the diagnosis is obvious, we inform the patient's wife of the situation and tell Mr. A. himself that he has a disease which is quite susceptible to x-ray therapy, but that treatment will have to be repeated from time to time. Consequently, after a day or so on a diet high in carbohydrates and sugar in order to prevent roentgen sickness (a possibility, by the way, which should never be mentioned to the patient), our radiologist administers 200 r at 200 K.V. peak through a 15 × 15 cm. lateral portal to the spleen. As this dose is well tolerated, similar treatments are given on successive days until a total dosage of 600 r is reached. Upon completion of his course of therapy Mr. A. goes home and is told he may do anything he feels like doing. No medicine is prescribed.

Eight weeks later our patient comes back for observation. proud of having gained 10 pounds, and feeling better than he has in several years. The spleen now extends only to the costal margin; the white count is 20,000 per cubic millimeter. A few myelocytes are still present in the smear, but aside from

this, the blood looks fairly normal. Since there is no immediate need for further roentgen therapy, we advise him to resume his normal activities and to return later for examination.

During the next few months Mr. A. reports at intervals of six to eight weeks. We note at each visit a gradually rising white count, an increasing immaturity of the leukocytes, and a slowly enlarging spleen, but since he feels perfectly well, treatment is withheld. About the sixth or seventh month after the completion of the first series of treatments, however, the white count has again reached 75,000 per cubic millimeter, and from past experience we know that the old symptoms of fatigue and sweating will shortly make their appearance. Therefore, another course of therapy similar to the first is advised and administered—its effect on the spleen and white count being essentially the same as that produced by the first course.

For the next two years Mr. A. continues to work, enjoys golf, and feels in every way normal, with the exception that on one or two occasions he states he has suffered for several days from a "pleuritic" pain in the left lower chest and a nagging dull ache in the left shoulder. (Symptoms such as these are obviously produced by infarcts of the spleen and have no great significance.) Nevertheless, as time goes on, we observe that the results of radiation are less marked; after treatment the spleen does not diminish in size as it did in the earlier phases of the disease, the white count rises more rapidly, and treatments must be given with greater frequency.

In the latter part of the third year of his illness, we find the effect of radiation lasts a scant two months. Within a short time an abrupt change takes place in his condition. An occasional purpuric spot appears on the legs; fatigue and exhaustion become prominent symptoms; splenic pain troubles him; a slight fever is detected from time to time. The spleen, now at the level of the umbilicus, no longer regresses with treatment: the red corpuscle count gradually declines to a level of 3,000,000 per cubic millimeter; the white count re-

mains elevated at the 50,000 level or above and resists farther reduction; myeloblasts appear in greater numbers in the stained smear, and the platelets become scarcer. Therapy no longer produces clinical or hematological improvement. Three weeks or so after the final treatment, Mr. A. takes to his bed. He now shows considerable emaciation; purpuric spots crop out on the arms, legs, and trunk, some oozing of blood occurs from the gums; a small area of gangrene appears in the mouth; scattered râles may be heard at the bases of the lungs; and, finally, a continuous low-grade fever and a rapid pulse herald the end. His wife inquires about blood transfusion, but we inform her that it would not only do no good but might make her husband more uncomfortable. Thus, approximately three years from the beginning of his first symptoms, after a period of four or five weeks in bed, our patient finally succumbs to his illness.

The foregoing description depicts the ordinary course and usual findings in an uncomplicated case of chronic myelogenous leukemia. Lack of time forbids a full description of all its possible clinical manifestations, but brief mention of certain ones might be made. In some instances the course is either shorter or longer than the one given here. For example, one of our patients has been known to have had the malady for at least eighteen years, and, although treated at rare intervals, she is still living and enjoying an active life. At times divergence from the classical blood picture is encountered. We have now under observation two examples of the disease accompanied by polycythemia, each with red cell counts above 7,000,000 per cubic millimeter. Similarly, variations in the physical findings occur at different stages of the malady. Some patients develop leukemic retinitis, others failing hearts; some may show no purpuric manifestations before death. others, on rare occasions, may exhibit infiltrations of the neoplastic tissue into the skin. And finally, while in our experience ascites is not infrequently a terminal event, priapism—so frequently mentioned in the textbooks—we have observed only once.



In summary, the diagnosis offers no difficulties, the prognosis for at least two years of comfortable life is excellent, and, although arsenic in the form of Fowler's solution is recommended by some, in our opinion high voltage x-ray therapy as often as may be indicated in each individual case is the therapy of choice.

#### ALEUKEMIC MYELOGENOUS LEUKEMIA

A woman, let us say in her early fifties, enters the hospital for study. The diagnosis of pernicious anemia has been made, but she has failed to respond to adequate doses of liver. Her story is one of several months' weakness, exhaustion, dyspnea, palpitation and increasing pallor. Perchance she may have had short periods of fever. No other significant information is obtained either from her or from her anxious family. When we examine her, we note the marked pallor, the presence of a few petechiae on the shins, and a spleen palpable possibly 6 to 8 cm. below the costal margin.

Examination of the blood reveals a puzzling picture. The white count is 4000 per cubic millimeter, the red blood corpuscles 2,500,000 per cubic millimeter, and the hemoglobin 60 per cent—a color index sufficiently high to justify a suspicion of pernicious anemia. A stained smear, however, shows certain unusual features. As in pernicious anemia, the red cells are on the average somewhat larger than normal, are well filled with hemoglobin, and exhibit considerable variation in size and shape, but the platelets are definitely fewer in number than we should expect in that disease. Moreover, the polynuclear cells, instead of showing aged forms (5 or 6 lobes), are, on the whole, quite young; a few myelocytes are present, and careful search may disclose an occasional myeloblast. We suspect aleukemic myelogenous leukemia and feel more certain of that diagnosis when the basal metabolic rate is found to be plus 40 per cent.

In order to settle this important question, that of a disease with a fatal prognosis, a surgical colleague performs a biopsy on the sternal marrow; and when the pathologist re-

ports "myelogenous leukemia," or "aleukemic myelosis," our diagnosis, suspected from the examination of the blood smear, is verified. In retrospect, we recall that the spleen seemed too large and the petechiae somewhat unusual for pernicious anemia, but admit that the diagnosis could not have been made with any certainty without the evidence obtained from the biopsy specimen.

In contrast to the classical type, in this form of the disease the prognosis and indications for treatment are by no means obvious. Length of life varies from a few months to one or two years, and on occasion a patient may live five or six years. In general, however, aleukemic myelogenous leukemia has a shorter course than the leukemic form of the disease; but, so far as I know, there are no signs which enable one to predict with any degree of accuracy how a particular patient will behave. Treatment, too, is more difficult to plan. Seldom producing brilliant results, high voltage x-ray therapy to the spleen, nevertheless, is always worthy of trial. More often than not it is injurious, at times producing a greater degree of anemia, or even enhancing the purpuric tendencies, but the same undesirable results may also be seen after blood transfusions. There is a possibility that "spray irradiation" of the whole body may prove of value in certain cases; at the present time, however, this type of x-ray therapy has not yet been adequately investigated. We can only conclude, then, that each case of the disease requires individual handling. The most important fact for the medical attendant to remember, particularly when faced by insistent relatives, is that it is incumbent upon him to avoid making his patient worse by ill-considered therapeutics.

#### CHRONIC LYMPHATIC LEUKEMIA

Miss H., a spinster, possibly forty-two years of age, comes to us because of the presence of enlarged glands in the neck and groins. She admits these tumors first appeared about a year ago, but since they were nontender, painless, and stationary in size, Miss H. did not consult a doctor. During the

past four months, however, a loss of 5 pounds in weight, increased fatigability, gradual enlargement of the glands, and disturbing comments of friends finally induced her to seek medical advice. A more detailed inquiry into her medical history fails to account for these swellings, and adds no facts of importance.

Upon examination, our patient, in addition to showing moderate pallor, exhibits enlargement of the glands on both sides of the neck, in each axilla, and in each groin. In each site they range from 6 to 10 in number, and vary in size from 1 to 4 cm. Their consistency is firm, elastic rather than hard, and they move freely beneath the skin. An enlargement of the spleen is present, this organ projecting 6 cm. below the costal margin.

Examination of the blood reveals a red corpuscle count of 3,500,000 per cubic millimeter, the hemoglobin is 60 per cent, and the white cell count 100,000 per cubic millimeter. A stained smear shows that 90 per cent of the white cells are small lymphocytes, relatively normal in appearance. The red cells exhibit moderate variations in size and shape; the platelets are somewhat diminished in numbers.

With the diagnosis of chronic lymphatic leukemia thus established, we repeat to Miss H. what we said to the patient with chronic myelogenous leukemia, and plan our high voltage x-ray therapy as follows: 600 r through adequately sized fields (ordinarily  $10 \times 10$  cm.) to each group of glands in the neck, axillae, and groins, and the same amount, through a larger field ( $15 \times 15$  cm.), to the spleen. Under ordinary circumstances this amount of irradiation will bring about marked regression in the size of the tumors, and will reduce the white count to less than 25,000 per cubic millimeter. Occasionally certain sites will require more therapy than here outlined; usually, however, they may be further treated with safety, since the effect of roentgen therapy on the white count in this disease is not so marked as in the myelogenous type.

After the initial course of treatment, the patient returns for observation at intervals which vary in length according to the

circumstances of the case. But since in this disease the blood is not the sensitive indicator of the need for therapy that it is in myelogenous leukemia, decision in regard to treatment must be based on other findings. Because some patients feel well with a leukocytosis of 75,000 per cubic millimeter, others miserable at a level of 20,000, the general feelings of the individual in conjunction with the complete physical findings are of more importance than the condition of the blood. In some instances sarcomatous infiltration takes place into the skin, subcutaneous tissues, bones, nervous system, conjunctivae, tonsils, pleurae, stomach, liver (with jaundice), kidneys, prostate, or testes. Regardless of the site, such abnormal tissue should be adequately irradiated. The dermic form of the disease, *mycosis fungoides*, which is merely a lymphoblastomatous neoplasm first manifesting itself in the skin, frequently exhibits a leukemic blood picture in its later phases, and as such, should be treated as an ordinary case of lymphatic leukemia. Obviously, then, there are no hard and fast rules applicable to every case. Each must be regarded as a separate problem.

The length of life from the onset of the first symptom varies remarkably from one case to the next. As a general rule, the disease seems more *benign* in patients over sixty-five than in those under forty-five. In this clinic we have observed patients who have lived only six months, others who have lived nine to ten years. Yet, you must be warned that a prognosis derived from the first clinical impression is not always correct. As an example of this, the following instance comes to mind. Two years ago, a patient, apparently moribund, whose symptoms had appeared only eight weeks previously, was given unusually heavy irradiation through large fields to the chest and abdomen despite the fact that he showed ascites, general anasarca, and pulmonary edema. Three months later, he had recovered sufficiently from his malady to go on his annual duck shooting expedition. At the present time he is still living and carrying on his business.

## ALEUKEMIA AND PSEUDOLEUKEMIA (LYMPHATIC TYPE)

Since the pathologic histology of all three conditions is the same, the terms *lymphatic leukemia*, *aleukemia*, and *pseudoleukemia* do not define separate diseases, but designate clinical variations of a single morbid process. The qualifying term *aleukemia* has been applied to those cases with normal or subnormal total white counts that have a lymphocytosis above 60 per cent; *pseudoleukemia*, to cases that show no definite evidence in the peripheral blood of the neoplastic process going on in the lymph glands and spleen. That all of these conditions are phases of lymphatic leukemia is illustrated by one of our former patients, who, during seven years' observation, passed from the leukemic, through the aleukemic, and into the pseudoleukemic phase in which he died. Preferably, we should employed Mallory's designation of "lymphoblastoma" to include all tumors arising from the lymphocyte, and should add to it the necessary clinical qualification, *e. g.*, "lymphoblastoma aleukemicum."

As we have seen, lymphatic leukemia is readily diagnosed from the blood examination alone. Usually in the aleukemic phase, the peripheral blood enables us to be certain of the diagnosis, but on occasion a biopsy is necessary. In the pseudoleukemic phase, however, a biopsy of a lymph gland is always required if we are to have our clinical impression confirmed.

Neither the course, prognosis, nor treatment of these two phases of the disease differs essentially from that of lymphatic leukemia. If anything, when we contrast either one with lymphatic leukemia itself, we are apt to find its course more bizarre, its prognosis more unpredictable, and its treatment more perplexing.

## ACUTE (MYELOBLASTIC) LEUKEMIA

We are called to see a boy eight years of age, who has been in bed for the past ten days suffering from weakness and fever. From the information at our disposal we obtain the following noteworthy facts: approximately four weeks ago,

the lad was put to bed by his mother for what seemed to be an ordinary attack of grippe. After a few days of malaise and fever, however, he recovered sufficiently to return to school. Soon thereafter, the mother noticed his lack of appetite and his unusual weariness, but she only became alarmed ten days ago when she realized how pale he had become. Upon finding a temperature of  $101^{\circ}$  F., the child was again put to bed, and since that time he has continuously shown a fever, his appetite has rapidly failed, and his pallor has become even more marked. Aside from a few bruises recently noted on the skin, the rest of the story gives us no essential facts.

On physical examination, our patient looks moderately ill, is quite pale, and shows a temperature ranging from  $99^{\circ}$  to  $101.5^{\circ}$  F. We observe a moderate number of petechiae on the skin of the limbs and trunk, several similar lesions on the mucous membrane of the mouth, and a few small bruises scattered over the legs and abdomen. With the ophthalmoscope we make out a few small hemorrhages into the retinae. On palpating the neck, axillae and groins, we note the glands in each of these regions are somewhat enlarged, the majority averaging 1 cm. in size. Examination of the abdomen shows the liver and spleen to be enlarged, the latter being palpable 4 cm. below the costal margin.

Our worst forebodings are confirmed by the examination of the blood. There is an anemia of 2,500,000 red blood corpuscles per cubic millimeter, and the white cell count is 70,000 per cubic millimeter. In the stained coverslip preparation, all of the white cells appear to be either myeloblasts or primordial cells too immature for classification, a few nucleated red cells are noted, and the platelets are practically absent. Yet, in spite of this grave disturbance of bone marrow function, the mature red cells seem to be fairly normal in size and shape. As one would expect with so few platelets, the bleeding time is strikingly prolonged. Hoping for the remote possibility that the disease might be an unusual manifestation of *infectious mononucleosis*, we send a specimen of serum to the nearest Wassermann laboratory for determination of the

heterophile antibody titer. (In infectious mononucleosis this is usually as high as 3 plus in a dilution of 1:64.) But in a day or so, the report returns marked "negative."

At this point someone is certain to raise the question of "acute monocytic leukemia." For all practical purposes, however, this is an instance of academic hairsplitting. Whether or not such a separate disease exists need not concern us, for the prognosis and treatment are no different than if the diagnosis be myeloblastic leukemia.

The prognosis in this terrible malady is not difficult to make. From the onset of symptoms the length of life is usually six weeks; occasionally a patient may live eight to ten weeks, but rarely longer. Few diseases in the field of medicine have a 100 per cent fatality such as this, and fewer still have such a sharply defined course. Toward the end, the anemia becomes more marked, the purpuric tendency more manifest, and often there occurs gangrene of the buccal cavity. The white count frequently becomes lower, and on occasion the terminal blood picture may simulate agranulocytosis.

All specific treatment is futile. x-Ray therapy practically always makes the patient worse. The use of blood transfusions and arsenic preparations is to be discouraged, for neither agent produces with any consistency even temporary benefit. Obviously, then, when faced with a situation of this sort, the medical attendant should try to make the patient as comfortable as possible, and should do all in his power to convince the family of the importance of doing nothing. The first is solved by employing a good nurse, the second by utilizing the services of consultants.





## CLINIC OF DR. HENRY JACKSON, JR.

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### NOTES ON THE TREATMENT AND PROGNOSIS OF HODGKIN'S DISEASE AND ALLIED DISORDERS

OUR present-day treatment of Hodgkin's disease is admittedly inadequate, yet we must acknowledge that dramatic remissions, often of long duration, may be brought about even with the limited therapeutic measures at our disposal. The prognosis is conceded to be grave, yet it is undoubtedly true, in certain instances at least, that the disease runs a benign and chronic course of many years' duration. We must not allow our pessimism to prevent persistent and relentless treatment even in the face of apparently hopeless odds. Many patients who appear to be well nigh moribund may, by appropriate measures, be restored to some degree of health and in rare instances, though the diagnosis appears, from biopsy, to be certain, the patient may live for many years undisturbed by the underlying condition.

The following cases serve to illustrate this thesis.

Case I.—K. A. D., a twenty-year-old white, single man was admitted to the hospital May 25, 1936 (H. H. 36-542.) A year before entry the patient had had a mild upper respiratory infection following which there had appeared an enlarged lymph node in the right neck. There was no impairment of general health. The node was neither painful, red nor hot yet it persisted after subsidence of the respiratory infection. Eight months later his family noticed that the patient was becoming pale. For several weeks before admission, he had been running a septic type of temperature and had had many rather

severe, drenching night sweats. Shortly thereafter there appeared edema of the ankles and scrotum and, coincidentally, both his hearing and vision began to fail. He had several severe nosebleeds.

The past and family history were irrelevant.

Physical examination, on admission to the hospital, showed a poorly nourished, emaciated, young man lying apathetically in bed. He appeared to be in extremis. His vision was markedly impaired. General objects he could distinguish but even the largest newspaper type could not be read. The left pupil was much larger than the right. Both reacted well to light and distance. The left eye showed a moderate degree of enophthalmos and was deviated downward and inward. The right fundus showed several patches of exudate similar to that seen in chronic nephritis and, in addition, a large area of chorioretinitis on the temporal side of the disk. The left fundus showed a high degree of optic atrophy. In neither ear could he hear the tick of a watch. Both nostrils were filled with clotted blood and his lips were parched, cracked and bleeding. In the right neck, from the angle of the jaw to the supraclavicular space, were many firm, nonadherent lymph nodes averaging about 2 cm. in diameter. Recently, there had been excised from this region a lymph node, the examination of which showed the typical picture of the sclerosing type of Hodgkin's disease. In each groin were large numbers of firm, tender lymph nodes. Many similar nodes could be felt deep in the pelvis, above the pelvic brim. The heart was normal in size. Signs of moderate ascites were present, but neither liver nor spleen could be felt. There was marked edema of both legs and of the scrotum and penis. The red blood cell count was 2,130,000 per cubic millimeter; the hemoglobin 30 per cent; the white blood cell count was 2000 per cubic millimeter; the platelets were greatly diminished. The differential white blood cell count was normal. The urine contained a small trace of albumin and a few red blood cells. The temperature was 103° F. The pulse 130.

The disease obviously involved the central nervous system, ears, eyes, chest, abdomen, pelvis, bone marrow and peripheral lymph nodes. It would be difficult to find an instance of more widespread involvement. Rarely does one see a patient in more dire straits. His condition seemed, indeed, desperate and it was decided to give several blood transfusions before instituting x-ray therapy. In addition, he was put on a liberal, high caloric diet and given 3 drops of a special viosterol containing 1,000,000 international units per cubic centimeter.

Between May 26th and June 11th, three blood transfusions, totaling 1600 cc., were given with the result that the hemoglobin rose to 50 per cent and his red blood count to 3,500,000 per cubic millimeter. During the interval his general condition remained essentially unaltered, but, interestingly enough, his hearing improved sufficiently so that he could hear a watch tick in either ear and could understand normal conversation. His eyesight had similarly improved though not to the same extent. His condition now appeared to warrant the institution of x-ray therapy and inasmuch as the most marked lymph node involvement was in the pelvis, radiation was directed to that area and from June 11th to June 15th, he received 275 r units of high voltage x-ray. He suffered no untoward reaction to this small amount of radiation so that

between June 15th and June 22nd he was given 1000 r. units to the abdomen. His temperature remained elevated, the physical examination was essentially unaltered and his general condition seemed, if anything, rather worse. He became jaundiced and, even during the day, he was somewhat drowsy. He took no notice of his surroundings and was, with some difficulty, aroused from his almost constant lethargy. The red blood cell count had fallen to 1,940,000 per cubic millimeter and the hemoglobin to 32 per cent.

The outlook was certainly not bright; all therapeutic measures to date appeared to have been unavailing. In view of the falling red blood cell count he was given, between July 1st and July 10th, 2000 cc. of blood intravenously with a resultant rise of the red blood cell count to 3,480,000 per cubic millimeter. By this time his temperature had come down to normal, his hearing was perfect and his eyesight, though still poor, was much improved. He was allowed up and around the ward within the limits of his strength. His appetite, on admission practically nil, was now ravenous. His general condition improved daily. He rapidly gained both strength and weight. The emaciated, apathetic boy first seen became an optimistic young man. The lymph nodes in all areas became very much smaller. The ocular manifestations improved with the exception of the retinal changes which remained unaltered. The peripheral edema and ascites had disappeared. On July 20th he was given another blood transfusion of 500 cc. and on July 25th he walked out of the hospital to return to his home.

There would seem to be no question but that the many blood transfusions—a total of 4000 cc.—played a major rôle in this patient's recovery and it has been our general experience, especially in patients running high temperatures, that transfusions are highly beneficial. The influence of the viosterol is, of course, problematical, but it has been our feeling that it is helpful. Radiation must, of course, be used but blood transfusions and other general therapeutic measures are important adjuvants.

Case II.—J. A., a nine-year-old boy was admitted to the hospital August 22, 1935 (H H 35-931.) One year before entry there had appeared enlarged lymph nodes behind the left ear. For six months he had suffered from weakness and anorexia. Four months before entry more lymph nodes had appeared on the right neck and these had gradually increased in both size and number. For the past six weeks he had been running a temperature ranging up to 104° F. and had suffered from vertigo, headache and rapidly increasing pallor. On admission he was found to have a temperature of 105° F. He was very weak, trembling and sweating profusely. The skin and mucous membranes were extremely pale. In the right cervical region were many firm lymph nodes from 1 to 3 cm in diameter. The lungs were clear. The heart was normal in size. The apex beat, however, was very forceful and diffuse. The cardiac rate was

His temperature once more abruptly receded and he was discharged well, active and without abnormal findings on July 27th.

There again we have an excellent example of what transfusions plus repeated radiation can accomplish. In September he was desperately ill, anemic, jaundiced, edematous, with an enormously enlarged heart, a spleen below the umbilicus and a temperature of  $104^{\circ}$  F. A year later his physical examination was entirely normal and he was able to participate in all the normal activities of his age.

The average duration of Hodgkin's disease is probably in the region of three years; but the outside limits are extreme. Many cases, particularly of the sarcomatous type, die within a few months from the onset of their symptoms, but on the other hand, a few cases survive many years, some with, some without, signs of the disease. When a case may be said to be cured is a matter of debate. Some authorities believe that all cases eventually succumb to the disease. An osteogenic sarcoma, surviving amputation and free from all signs of recurrence three years later, may properly be said to have been cured. Hodgkin's disease, on the other hand, may lie dormant for many years, only to flare up and run a rapid course to a fatal termination in a few months. In other instances, however, the disease early appears to be restricted rather sharply to a certain area and this fact, together with the knowledge that certain pathological types appear to run a benign course, justifies the hope, at least, that if the condition be attacked early and with vigor, a cure may be effected. The following cases of Hodgkin's disease or reticulum-cell sarcoma—a disorder probably closely allied and clinically often indistinguishable—illustrate this point.

Case III.—T. H., a seventeen-year-old boy, was admitted to the hospital on August 20th, 1920. (S-20-1522.)

Five years before entrance he had noticed small, painless lymph nodes in the right neck above the clavicle. These had gradually grown in size and in number to the time of his admission to the hospital. His past history was uneventful. There were no symptoms referable to the enlarged nodes. Physical examination, on entrance, showed no abnormalities except in the right neck

Here was found an enormous mass of firm, nonadherent, nontender lymph nodes, the whole mass approximating the size of a grapefruit.

On August 22, 1920 the mass was completely excised. All involved nodes appeared to have been accessible and were removed. Examination of these lymph nodes showed the typical picture of Hodgkin's disease. (S-20-1522.) The patient was unfortunately told by one of his friends that he would die in six months. As a respite from this gloomy outlook he had recourse to hard liquor in large quantities. At the end of a year he found himself noticeably alive but unable to forego his alcohol. To date, October, 1936, sixteen years later, he has had no signs of recurrence even though examined repeatedly and carefully, but he has had but scant success in combating the alcoholism. He may, I believe, be regarded as cured.

Case IV.—L. C., a thirty-six-year-old woman, was admitted to the hospital in April, 1936 (Lo. Cl. 1936). In 1910, at the age of thirteen years, enlarged lymph nodes had appeared in the right neck. These had been removed at another hospital and had been diagnosed as Hodgkin's disease. The sections have but recently been reviewed by the pathologist and by ourselves and there can be no question but that the diagnosis is correct. She remained entirely well until 1917 when the lymph nodes recurred. Again they were removed and again (S-17-367) they showed the typical picture of Hodgkin's disease. No further signs or symptoms occurred until two months prior to her last admission, when, once more, the lymph nodes appeared in the right neck. Physical examination revealed no abnormalities except that in the right neck beneath the upper third of the sternomastoid were a group of firm, freely movable nodes. These were excised again and showed (S-36-1256) the picture of Hodgkin's disease.

For twenty-six years she has harbored the condition known as Hodgkin's disease, yet she still remains in excellent general health.

Case V.—W. J. B., a forty-four-year-old white man, was admitted to the hospital, October 8, 1924 (M. G. H. 265742). Ten months before admission he had noticed some pain at the lower end of his right humerus. He was treated with ultraviolet light by his personal physician with much relief. Five months before admission, while throwing a baseball, he experienced a sharp, stabbing pain in his right arm and found himself unable to flex his arm at the elbow. A *Rays* showed a fracture but there was evidence of tumor. He was, therefore, treated conservatively and he recovered, to some extent, the use of his arm. In August, 1924, five months later, it was noted that the fracture was unhealed but it was not until October that an x-ray diagnosis of malignancy was finally possible, and on October 9, 1924, the right arm was removed at the shoulder by Dr. C. C. Simmons to whom I am indebted for this case report. The entire humerus was virtually destroyed by tumor from one end to another. The sections showed typical reticulum-cell sarcoma (S-24-10-56).

The patient remained well until October, 1931—seven years later—when

there was a recurrence in the skin near the point of amputation. This was widely excised and the patient is, to date (October, 1936), alive and well without any signs or symptoms of recurrence, twelve years after the amputation. In view of the extraordinary degree of involvement of the humerus and the comparatively long delay between the first symptom and the amputation, the result must be regarded as extraordinarily good and would further, it seems to us, argue for the occasional, isolated nature of the disease. It is difficult to believe that with such extensive disease the patient could be alive and free from signs and symptoms twelve years later had the pathological process originally been, in reality, widely disseminated.

These examples could be multiplied several fold and it would be well to bear them in mind in considering the choice of treatment in a given case. That in the vast majority of instances of Hodgkin's disease, reticulum-cell sarcoma and lymphosarcoma, the process, when first seen by the physician, has involved more than one area of the body, is not to be denied, but that in some, at least, the disease may start from, and be limited to, a given focus, is indicated by such instances as are referred to above. It is unfortunate that by the means now at our disposal the pathological changes cannot be more surely detected in their early stages. In the majority of instances Hodgkin's disease is, at onset, painless—as are many cases of reticulum-cell sarcoma. Were osteogenic sarcoma essentially a painless disease the number of true cures would be vanishingly small. Were Hodgkin's disease, essentially and in its early stages, painful, the number of true cures would, unquestionably, be greater.

**Summary.**—*x*-Ray therapy probably does not, on the average, materially prolong life in Hodgkin's disease, but persistent treatment, especially when combined with blood transfusions and viosterol in large amount, can produce marked and lasting benefits even in those patients who appear virtually moribund when first seen by the attending physician.

In certain instances, Hodgkin's disease and reticulum-cell sarcoma would appear to be a localized condition in its early stages. Radical measures, undertaken early, offer, in these instances, a very real hope of permanent cure.

## CONTRIBUTION BY DR. ROGER I. LEE

BOSTON

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### A CASE OF POLYCYTHEMIA VERA OR ERYTHREMIA

THIS patient, age fifty-five, presents himself on account of very general symptoms. He cannot tell when his first symptoms began. He thinks it was a matter of years. Apparently, there has been a gradual increase in these symptoms and there has been some punctuation with severe headaches which are increasing. These indefinite symptoms, of which he complains, consist of "feeling tired," "waking up tired," and "going to bed tired."

As you perceive, he is a very intelligent man. He is, by profession, a minister. Despite his rather extensive vocabulary, he cannot further describe his symptoms. He finds it increasingly hard to carry on his profession. He finds physical, nervous and mental efforts equally trying.

He states that all the members of his family, on his father's side, have been full-blooded and very ruddy people. His father and grandfather were both of this same appearance, and this seems to be true of his 3 brothers, although he is the ruddiest of them all. I know casually these brothers and, as a matter of fact, I made blood studies of 2 of them and those studies have been negative. This man, although married, has no children and, curiously enough, two children of one of his ruddy and apparently plethoric brothers are especially pale and pasty.

It is true that complexions, such as ruddiness, amounting, in this case, to an appearance of plethora in the lay sense, have a marked tendency to run in families. The patient volunteers the information that his family, as a family, is sparing of food and drink. He himself is essentially a teetotaler, as

far as alcohol is concerned and, yet, his ruddy complexion would suggest overindulgence in red meat, the ales and wines.

Our patient feels that his correct diagnosis is that he is "full-blooded," and he believes that his headaches are due to too much blood in his head. He has said that he would be better for bleeding and has expressed the wish that he lived in the days when bleeding was a common method of therapy.

There is one other symptom which he finds very distressing and that is priapism which occurs at irregular intervals and is of irregular duration and, moreover, is not relieved by masturbation or intercourse with or without ejaculations.

The essential facts of his physical examination confirm the impression which our eyes give us. The retina is congested. Large and engorged veins can easily be seen. As one scrutinizes the skin of the nose and the mucous membranes of the nose, mouth and throat, one sees this same tendency to engorgement and the presence of easily visible bluish capillaries. The heart is not enlarged. The blood pressure is not particularly elevated. In his case, it is 145/90. The spleen is definitely enlarged and easily felt. There is no edema. Of course, the main interest is in the blood condition. We find his red count to be 11,000,000, his white count 17,500. Hemoglobin reading is high, 120 to 130 per cent in this case, but the color index is under 1. The blood smear shows slight hypochromia. There are normoblasts and megaloblasts present, but the differential count is not significant. The blood platelets are moderately increased. The blood volume in this case, as in all others, is definitely increased. It is about two times normal. The clotting or coagulation time of the blood is slightly delayed. The bleeding time is normal. The resistance of the red cells to the varying strengths of solutions of sodium chloride is so close to normal as to require no comment. His urine is often free from albumin and sometimes contains a small amount of albumin and at times a few casts. There is no fixation of the specific gravity of the urine. The Wassermann test is negative. The blood chemistry is not significant.



The diagnosis in such a typical case presents no real difficulty. There are times when the diagnosis may present a considerable problem. There are the borderline cases in which the elevation of the red count is not so high as in this case, but may be, let us say, between 6,000,000 and 8,000,000 reds. As a matter of fact, our normal figures have increased of late and we do not think that a red count of 6,000,000 is unusual in a male. These milder forms of polycythemia or erythrocytosis, which is the term applied to the secondary forms of polycythemia in contrast to the term of erythremia which is the term applied to the so-called "primary" polycythemia vera as described by Vaquez, Osler and others, do not, as a rule, present symptoms derived from the polycythemia but only symptoms derived from the underlying condition. Of course, it is true that we do not make so much distinction nowadays between primary and secondary forms of disease because it is likely that all cases of polycythemia are secondary to something. The mild forms of polycythemia, that is with red counts from 6,000,000 to 8,000,000, are not uncommon in certain forms of heart disease, of lung disease, and in any form of anoxemia. The researches on Pike's Peak, in Peru, and in the Himalayas, have shown that there is a compensatory polycythemia at high altitudes in which the red count returns to normal numbers readily when the individual comes down to low levels. In these cases, there is not the complete picture of the so-called "primary" polycythemia or erythremia. There is no considerable increase in the blood volume. It is merely the compensatory increase in the red blood corpuscles to facilitate oxygen carriage. The cyanosis of congenital heart disease, of emphysema, and of anoxemia, for example, at a high altitude is rather different from the engorged, bluish, ruddy color of erythremia. Likewise, the spleen which is fairly constantly enlarged in erythremia, is rarely felt in secondary polycythemia. Indeed, the splenomegaly may be so great as to be the presenting symptom of erythremia.

Theoretically, a number of conditions can produce a rela-

tive polycythemia and actually we can see a relative polycythemia in acute diarrhea, especially cholera, in which dehydration results sometimes in enormous increase in the number of red cells. Sweating and pulmonary edema from gas at times produces a polycythemia. High red counts and high hemoglobin estimates are frequent in cases of shock without hemorrhage. Rarely, polycythemia may be found also as a result of certain poisons including histamine and some of the snake venoms.

Somewhat over two years ago, a man presented himself with sudden blindness. The examination of his blood showed that he had around 7,000,000 red cells. In rare instances, blindness has been observed in true polycythemia. It is true that this man was treated for polycythemia and that his eyes did recover but I never believed that there was any connection between the two.

Now that our patient has gone out, we may discuss his prognosis and treatment. The prognosis is inevitably fatal but it must be remembered that this is a chronic disease, the duration of which varies from several months to many years. In the true form of polycythemia, the usual duration, even after diagnosis, which is not usually established for over a year, is a number of years. In this patient, his diagnosis was made nearly two years ago and you will recall that the onset was insidious perhaps years before this. At that time, he had a red count just under 10,000,000 and it has run along without much variation since then. As a rule, the increasing weakness and disability progress slowly with a great many minor physical and minor mental symptoms. At times, headaches and attacks of dizziness may be very severe and there may be evidence of true cerebral accidents, as thromboses or hemorrhages. For one reason or another, the autopsy material on the cerebral lesions is not great. Vascular lesions in the brain and in the extremities, especially thromboses, are common. In some of the cases, which persist for many years, the terminal blood picture is that of myelogenous leukemia. Of course, at first, this suggests that the condition might be a

tumor involving the bone marrow which affects chiefly the red blood corpuscles but which may affect the myelocytic series as well. However, these findings are probably to be related to an alteration of output of bone-marrow cells or a change in the threshold of the marrow. The bone marrow in this disease is hyperplastic and this hyperplasia extends to the parts of the bone marrow system which are ordinarily yellow. Obviously, there is no benefit in the sternal biopsy which occasionally gives us so much information in other blood diseases.

**Treatment.**—The treatment is evidently unsatisfactory. Venesection will give temporary relief to the pressure headaches and some cases are kept fairly comfortable with repeated venesection. Phenylhydrazine, usually in the form of phenylhydrazine hydrochloride, given in doses of 0.1 Gm. is often helpful. While not all cases respond to phenylhydrazine and the dosage frequently requires considerable adjustment, nevertheless, usually the red count can be brought down to normal or below. It must be remembered, however, that this (as in the case of bleeding) relieves only the symptoms of plethora. The disease progresses as does the weakness. However, treatment with phenylhydrazine has much to recommend it. It is easily carried out. Repeated bloodletting is often objected to by the patients. Irradiation therapy obviously requires the patient to travel considerable distances to secure an adequate therapy apparatus and an expert who can make the difficult calculations on which the treatment depends. At the moment, in the large medical centers, x-ray therapy to the bones is being largely employed. The exact procedure is quite complicated. The white count is used as a standard of treatment and at a certain low point, such as 3000, the treatments are discontinued.

This man has had no treatment at all because he has not seemed, until now, to present symptoms which would warrant treatment. On the other hand, the headaches increasing in severity suggest that he may be having thromboses. Certainly, the priapism he finds peculiarly distressing. It is planned to give him some rather prolonged x-ray treatments

but this is done without particular enthusiasm. Phenylhydrazine might be used or bloodletting might be equally effective.

One cannot escape from the conviction that there is a large family element in this condition. The gradations of severity of the disease in certain families is against the idea of tumor in any ordinary meaning. When the disease has established itself as a definite entity, it runs a very progressive, even if a chronic course. It would seem reasonable to suppose that a polycythemia vera, or erythremia, is secondary to some substance or condition. This substance or condition is not a recognizable form of anoxemia. The only thing in common, between the erythremia and the so-called "erythrocytosis," is the high red count.

## CLINIC OF DR. R. CANNON ELEY

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### HEMOPHILIA\*

It is well recognized that individuals with hemophilia have a much more stormy course during early life than at any other time. This is probably due to the fact that older patients are more careful and avoid those hazards which seem to be such an integral part of the life of a young boy. It is during this early period that the more serious, and often fatal, situations arise—a truth which is well supported by the relatively small number of adults with hemophilia in comparison to the number of children with the same condition. This afternoon I would like to discuss this disturbance with you, call your attention to the various therapeutic measures which have been employed and present some of the patients whom we have treated.

This condition was first described by Otto<sup>1</sup> in 1893 and at that time attention was directed to the fact that the disease manifested itself clinically only in the male and was transmitted by the female. Following this report, various writers<sup>2, 3</sup> suggested that it not only could but did appear as a clinical disturbance in the female. However, Bullock and Fildes<sup>4</sup> in 1911 published the results of their studies on this aspect of hemophilia and concluded that the disorder occurred only in males and was transmitted by the female (Nasse law<sup>5</sup>). Further support of this "law" has been offered by Klug<sup>6</sup> who has recently restudied the Manpel family and has shown that

\* This study was supported in part by a grant from the Commonwealth Fund of New York.

through six generations the disease has been transmitted only by the female members. Davidson and McQuarrie<sup>7</sup> have reported similar statistics in eight generations of a family. However, that transmission is entirely limited to the female seems open to question as both Legg<sup>8</sup> and Mills<sup>9</sup> have presented evidence which would indicate that in rare instances the male may transmit to the female and she in turn to her children. If a man with hemophilia marries a woman who is not affected, his sons and his grandsons will not inherit hemophilia. However, should there be daughters by this marriage, they will be able to transmit the disturbance to their sons, and their granddaughters will in turn be "carriers." Theoretically it is possible for a woman to manifest hemophilia as a disease provided her father had the clinical manifestations and her mother was able to transmit it. From Macklin's<sup>10</sup> studies it would appear that the only individuals in a family afflicted with hemophilia who may marry without fear of transmitting it are the *unaffected males* and, of course, their descendants.

**Symptoms.**—Although the outstanding symptom of this disease is hemorrhage, yet it rarely manifests itself clinically before the first part of the second year of life. However, profuse and even fatal bleeding may follow such simple surgical procedures as circumcision or severing of the frenulum of the tongue during the first few days of life. The tendency to bleed not only varies with different individuals but may vary in the same individual; that is, on one occasion he may bleed very little from a moderately severe laceration while at another time a minor abrasion may prove fatal. The reason for this variation in the same individual remains unexplained although it has been pointed out that hemorrhage appears to occur more frequently during the presence of an infection than at any other time.

Trauma practically invariably precedes the appearance of hemorrhage. The injury necessary to produce bleeding, however, is very slight and not infrequently one is unable to obtain any history of trauma as the patient does not consider the usual slight blows as of significance. Since trauma does pre-

cede hemorrhage, it naturally follows that the clinical manifestations will vary according to the point of injury. Superficial or cutaneous lesions usually appear in the form of small or large hematomas and at times may prove incapacitating as well as painful. One of the most obstinate forms of superficial bleeding in epistaxis as this may persist for several days. Bleeding from loose or carious teeth is not uncommon and fatal bleeding may follow the extraction of a tooth. The viscera, with the exception of the kidneys, are rarely the site of bleeding and hemorrhage into the central nervous system is very unusual.

One of the most incapacitating forms of bleeding is hemorrhage into a joint. The development of an acute hemarthrosis is usually sudden and, as with other forms of hemorrhage, is preceded by trauma. If the hemorrhage is confined within the capsule there is no discoloration of the surrounding tissues. Associated with the local disturbance there is a mild systemic reaction characterized by an elevation of temperature, general malaise and a moderate polymorphonuclear leukocytosis. The duration of the hemarthrosis is naturally dependent upon the severity of the effusion but in the average case the swelling and pain subside within ten to fourteen days. However, with recurring attacks, chronic arthritic changes develop<sup>11</sup> and these gradually impair the function of the joint. The limitation of joint motion is not due to calcification but is the result of a fibrous ankylosis.<sup>12</sup> Atrophy of the musculature from disuse and the development of deformities are common complications among those individuals who have suffered from repeated hemarthrosis. At times these disturbances may be of such a severe nature as to preclude locomotion.

**Diagnosis.**—The diagnosis can usually be made without difficulty, as the family history, clinical course of the patient, and hematological studies immediately suggest the disease. However, during the first few days of life such conditions as hemorrhagic disease of the newborn, septicemia, congenital syphilis, and certain types of jaundice may prove confusing. Purpura haemorrhagica, a disorder which is more frequently

confused with hemophilia than any other disease may be differentiated by an examination of the blood. In hemophilia, the total number of platelets per cubic centimeter of blood is within normal limits, while in purpura (either symptomatic or idiopathic) the total number of platelets is usually reduced. Furthermore, the coagulation time and bleeding time of the blood are quite different in the two diseases.



Fig. 25.—Roentgenogram of the left knee showing arthritic changes. The joint space cartilage is almost completely eroded and there is a suggestion of slight cystic degeneration adjacent to the metaphyses of the medial condyles. There is also moderate diffuse bone atrophy. Several transverse striæ in the diaphyses proximal to the joint point to repeated periods of interference with growth during late childhood.

Although careful pathological studies of patients dying from hemophilia have been made, yet the underlying defect of the hematopoietic system has not been finally established. Time does not permit a discussion of the histopathology of this disease, but your attention is called to a recent publication by Custer and Krumbhaar<sup>13</sup> on this aspect of hemophilia.

The characteristic abnormality of the blood of these pa-



tients is the prolongation of the coagulation time of the venous blood. However, it should be noted that the coagulation time does not remain at a constant level but may vary from day to day, and may even show decided differences in the same patient within the course of twenty-four hours. Furthermore, the clotting time may even be within normal limits during a period of bleeding. There is also a variation in the coagulation time of the blood as obtained by venipuncture and that obtained by pricking the ear or the finger, a fact which necessitates the study of the coagulation time of the venous blood when any therapeutic measure is being tried as the coagulation time of the capillary blood is usually lower than that of the venous blood.

Fragility of the blood vessel walls, destruction of blood by toxins, and many other explanations have been offered as the cause of this disease. Howell,<sup>14</sup> Minot and Lee<sup>15</sup> *et al.* have suggested that although the platelets are normal in number yet they are more resistant, thereby failing to disintegrate rapidly enough to supply the necessary factor for coagulation; Klinger,<sup>16</sup> Addis,<sup>17</sup> Feissly and Fried<sup>18</sup> believe that disintegration of the platelets occurs in a normal manner. Eagle<sup>19</sup> has recently studied the various factors concerned in the mechanism of blood coagulation in individuals with hemophilia and has concluded that the platelets function normally. Mills<sup>20</sup> has offered evidence that the thrombin is not converted into prothrombin by the antithrombin. From these remarks it is apparent that there is no uniformity of opinion as to the underlying disturbance in hemophilia.

**Prognosis.**—Experience has shown that one must be careful in venturing an opinion as to the prognosis, as the slightest injury may prove fatal. Naturally, the possibility of longevity improves as the patient becomes older and is able to avoid those acts which may be accompanied by trauma. Although the coagulation time may not be markedly prolonged in all individuals with hemophilia, yet it would appear that the hazard as far as life is concerned is practically the same in all of these patients.

**Treatment.**—When one considers the numerous procedures that have been employed in the treatment of this disease, it at once becomes apparent that no one method has proved to be thoroughly satisfactory. However, before we consider any of these therapeutic measures, we might first consider what can be done to prevent its occurrence.

Since the only members of a hemophiliac family who may marry without fear of transmitting the condition are the *unaffected males* and their sons, it naturally follows that all females are potential "carriers" and therefore should not marry. In view of the fact that the only test as to whether or not the defect may be present is reproduction, the advisability of marriage and subsequent pregnancy becomes questionable. Sterilization before marriage, or the production of legal abortions should conception occur may at first glance appear rather drastic, yet when one stops to consider the seriousness of this disease and the most unfortunate clinical course of the patients, it soon assumes the cloak of respectability and saneness. However, if such measures cannot be employed, the nature of the disease should be impressed upon all those concerned.

Under *prophylaxis*, one should include the various forms of therapy that have been employed in an effort to reduce the coagulation time of the blood. Dietary régimes<sup>21, 22, 23, 24, 25, 26, 27, 28, 29, 30, 31</sup> of one nature or another have repeatedly been tried and have repeatedly been of no avail. Protein sensitization, first introduced by Vines<sup>32</sup> and subsequently elaborated upon by Mills<sup>33</sup> *et al.*, has offered a fairly satisfactory method for the control of oozing from superficial lesions; yet this procedure only affects the coagulation time of the capillary blood and does not reduce the coagulation time of the venous blood.<sup>34</sup> Even the value of this measure has been questioned by the negative results obtained by certain observers.<sup>35, 36</sup>

The observations of Birch<sup>27, 29</sup> in 1931 revived interest in the administration of ovarian substances as a possible means of reducing the coagulation time of the blood in these patients. The theory underlying this form of treatment has been based

on the generally accepted belief that the inherited trait depends on the behavior and character of chromosomes and that hemophiliacs are deficient in estrogenic substances. To date the value of this form of therapy has not been conclusively demonstrated, as various observers have reported both good<sup>39, 40, 41</sup> and poor<sup>42, 43, 44, 45</sup> results following the oral, subcutaneous, and intramuscular administration of ovarian substances. In fact, evidence has been presented which would indicate that these individuals not only possess adequate amounts of estrogenic substances but that they may even be present in excessive amounts. For many years tissue extracts, commonly known as "tissue coagulins," have been known to hasten the coagulation of blood. Schmidt,<sup>46</sup> Wooldridge,<sup>47</sup> Loeb,<sup>48</sup> Torraca,<sup>49</sup> and Mills<sup>50</sup> have repeatedly shown that such a substance could be obtained from practically every tissue in the body. The effectiveness of these coagulants has varied according to the locality from which they have been obtained. (Mills has demonstrated that an extract obtained from bovine lung has a greater potency than a similar extract obtained from other bovine organs.) Data has also been presented that would suggest that these coagulant extracts possess a certain degree of specificity for the species from which they are obtained.

In 1929, Sakurai<sup>51</sup> extracted normal human placenta and obtained a substance which when administered orally or subcutaneously reduced the coagulation time of the blood of animals. However, when it was injected *intravenously* the animals *died* as a result of intravascular coagulation. These observations, and the suggestion that tissue extracts might possess a certain degree of specificity for the species from which they were obtained, led Eley, Green, and McKhann<sup>52</sup> to investigate the possibility of obtaining a blood coagulant extract from the human placenta which might be more specific for humans than the coagulant extracts obtained from animal tissues.

The extract which has been obtained from human placentae has not only been shown to possess a strong coagulant property

but also to possess a certain degree of specificity for the species from which it has been obtained (Tabulation). Furthermore,

### TABULATION

COAGULATION TIME OF RECALCIFIED HUMAN OR BOVINE CITRATED PLASMA TO WHICH BOVINE LUNG COAGULANT EXTRACT OR PLACENTAL COAGULANT EXTRACT HAS BEEN ADDED.

	Time of coagulation.		
	Control.	Lung extract added.	Placental extract added.
Human plasma A.....	9'56"	1'45"	1'10"
Human plasma B.....	10'23"	2'04"	1'19"
Human plasma C.....	10'50"	2'05"	1'24"
Human plasma D.....	9'10"	2'08"	1'35"
Bovine plasma A.....	14'25"	1'00"	2'10"
Bovine plasma B.....	19'45"	1'45"	3'05"
Bovine plasma C.....	12'35"	1'25"	2'36"
Bovine plasma D.....	13'29"	1'10"	2'18"

To 1 cc. of plasma was added 0.1 cc. coagulant extract (containing 1.5 mg. N per cc., and 0.3 cc. of 2.5 per cent  $\text{CaCl}_2$ ).

*in vitro* experiments have shown that the extract coagulates hemophiliac plasma just as rapidly as it does plasma obtained from normal individuals. Nineteen children suffering from hemophilia have received this extract and in 12 cases there has been a reduction in the coagulation time of the venous blood to within normal limits. Of the 7 patients that did not respond satisfactorily, 3 showed a definite reduction while 4 failed to show any response (not all of those who failed to respond received intramuscular treatment). As this reduction only persists for periods of forty-eight to seventy-eight hours, it is necessary to continue the administration of the material over an indefinite period of time. Older children and adults have proved more difficult to treat than young patients and in certain instances no response has been obtained following either the oral or intramuscular use of the coagulant. It has not been used intravenously and caution should be exercised when it is injected intramuscularly as *the intravenous route may prove fatal*.

The following cases demonstrate the results which have been obtained with this form of treatment and from these it can be seen that although the coagulant has been effective in certain instances yet in others it has proved to be of no therapeutic value.

**Case I.**—The first suggestion that this boy might be suffering from hemophilia occurred when he was two weeks of age, at which time prolonged bleeding followed the retraction of the foreskin. However, the diagnosis was not

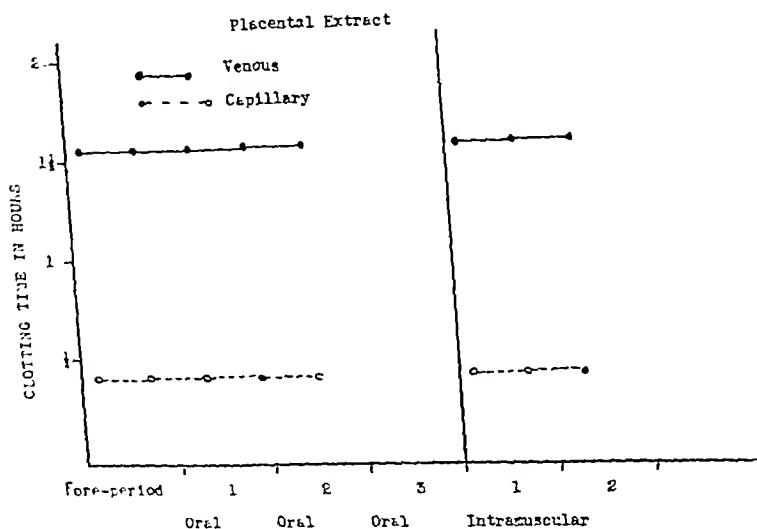


Fig. 26.—Diagnosis, hemophilia; age of patient four years; no family history of hemophilia; coagulation time of capillary blood, eighteen minutes; of venous blood, one hour and thirty-two minutes; no response following oral or intramuscular administration.

established until he was one year old. Since the age of eight months his clinical course has been typical of that seen in so many patients suffering from this disease. Hemorrhages following minor lacerations have necessitated frequent transfusions, hematoma of the subcutaneous tissues or muscles, and the development of hemarthroses have incapacitated him for long periods of time. In an effort to modify the course of the disease he was treated by protein sensitization and although there was a reduction in the coagulation time of the capillary blood, yet there was very little change in the clinical course. Placental coagulant extract has been administered by mouth, by rectum and by intramuscular injections without any appreciable alteration in either the coagulation time of the venous blood or in the course of the disease. In fact the

patient developed rather severe hemorrhages into one ankle and one knee during the period of observation.

**Case II.**—In contrast to the first patient, this boy did not present any clinical evidence of hemophilia until five years of age, at which time he developed an acute hemarthrosis of the right knee. It is of further interest to note that when he was three years old he developed acute anterior poliomyelitis with residual paralysis of the right leg and that at that time 5 lumbar punctures were performed without any abnormal bleeding from the puncture wounds

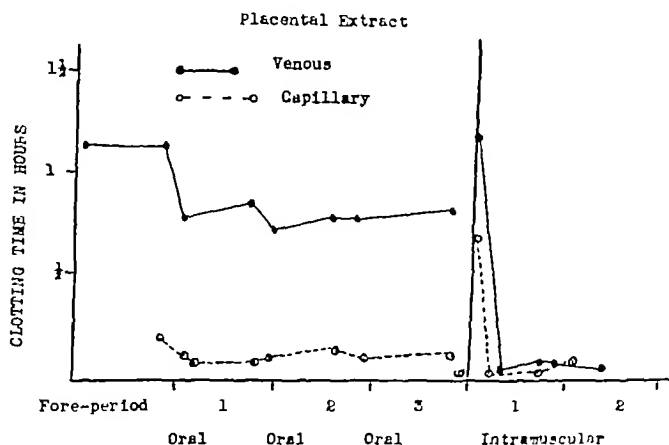


Fig. 27.—Diagnosis, hemophilia; age of patient twelve years; no family history of hemophilia; coagulation time of capillary blood, twenty minutes; of venous blood, one and one-half hours; no response following oral administration; satisfactory response following intramuscular administration

The clinical course of this boy has been characterized by repeated hemorrhages into his knees and ankles which in the course of time have produced chronic arthritic changes within the joints. The oral administration of placental coagulant extract was followed by only a partial response as shown by a retardation in the coagulation time from seventy-five to forty-five minutes. However there was a prompt and satisfactory reduction of the venous clotting time following the intramuscular administration of 5 cc of a sterile form of the coagulant.

**Case III.**—This sixteen-year-old patient apparently presented his first symptoms of hemophilia at the time of birth for at that time he bled so profusely from the umbilicus that it became necessary to transfuse him. Since early infancy he has suffered from repeated hemarthroses, numerous attacks of severe epistaxis and frequent hemorrhages from lacerations and carious teeth. Each of the arrows as shown in Fig. 28 represent an attempt to reduce the coagulation time of the venous blood by the oral administration of the coagulant extract, and as can be seen these attempts were only partially successful.

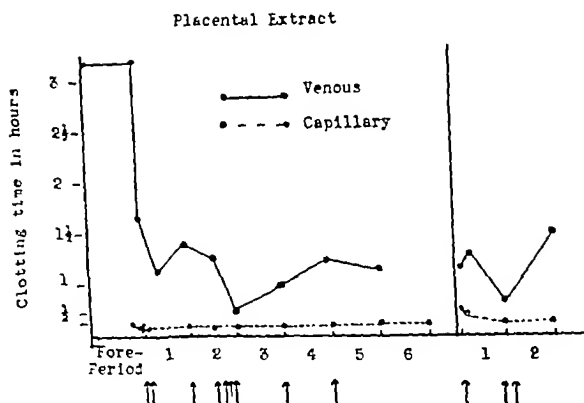


Fig. 28.—Diagnosis, hemophilia; age of patient sixteen years; brother died from hemophilia; coagulation time of capillary blood, twenty-two minutes; of venous blood, three hours and fifteen minutes; partial but unsatisfactory response following oral administration.

Whether more satisfactory results can be obtained following the intramuscular injection of the coagulant will be determined at a later date.

Case IV.—This patient was first admitted to the hospital when he was eighteen months of age. At that time he was bleeding profusely from a minor

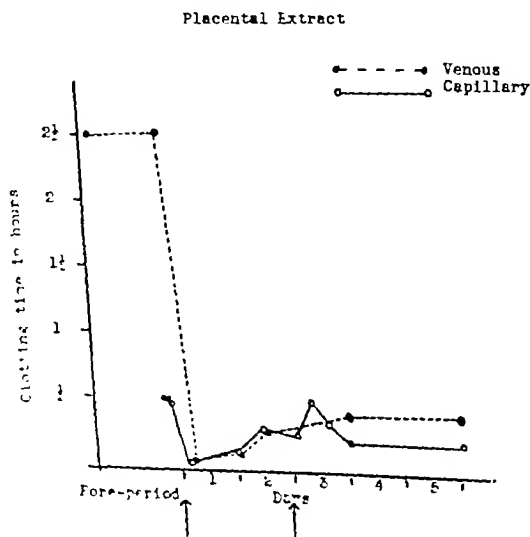


Fig. 29.—Diagnosis, hemophilia; age of patient, nine and one-half years; brother died from hemophilia; coagulation time of capillary blood, thirty minutes; of venous blood, two and one-half hours; satisfactory response following oral administration.

laceration of the lip and had to be transfused. His clinical course subsequent to that time has been marked by hemarthroses, repeated hemorrhages from slight wounds and frequent transfusions. Treatment by protein sensitization did appear to minimize bleeding from superficial abrasions but it failed to have any influence on the development of hemarthroses. Following the oral administration of 5 cc. of the coagulant extract there was an immediate reduction not only in the coagulation time of the capillary blood but also in the coagulation time of the venous blood. In order to maintain this reduction in the coagulation time of the blood it is necessary for this patient to take the extract every three days.

In treating *acute conditions* both local and systemic measures should be employed. If the bleeding site is accessible one may apply pressure or any of the various hemostatic substances which have been advocated such as tannic acid powder, Monsel's solution, cephalin, thromboplastin, fresh serum, etc. Hemorrhage from the kidney or from the gastro-intestinal tract are beyond such procedures. Systemic measures are usually more effective than local measures and these usually resolve themselves into one form of treatment, namely, transfusions of either whole blood or of citrated blood. In those instances in which acute conditions arise that require surgical interference one should carefully consider whether probable fatal hemorrhage is not a greater risk than the dangers of the disorder that has produced the surgical condition. Should the operation be considered as imperative, preoperative as well as postoperative transfusions should be employed.

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## CLINIC OF DR. CLARK W. HEATH

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### IRON DEFICIENCY IN GIRLS: CHLOROSIS

CHLOROSIS was one of the earliest forms of anemia to be recognized as a clinical entity. It was regarded as an anemia of adolescent girls, without definite etiology, responding remarkably to iron medication. It occurred commonly during the preceding century, particularly in city dwellers under poor hygienic conditions. The disease lent itself very well to flowery literary description. Naegeli,<sup>1</sup> who gave one of the more sober descriptions, and believed that inherited characteristics played an important part in the etiology, cited from the literature the following former opinions of the causation: an inborn functional hypoplasia of the blood; a tuberculous disposition: occult blood loss from the intestine or menstrual blood loss; intestinal putrefaction; gastroptosis; hypoplasia of the vascular system; a neurosis; insufficient protein breakdown in the liver. Chlorosis is still classified today in many textbooks of medicine as an idiopathic anemia. That it has largely disappeared during the present century has been a matter for comment and wonder.

Davidson and Leitch in their monograph on "The Nutritional Anaemias"<sup>2</sup> published in 1934 made the following valuable comment upon the causative factors in chlorosis and the reasons for its relative disappearance: "Although described as a primary anaemia in all textbooks of medicine, there can be little doubt that chlorosis was essentially a nutritional

anaemia, consequent on deficient iron intake. . . . A mild degree of hypochromic anaemia is apt to occur at puberty, but when growth slows down the iron intake of the diet is usually sufficient to produce a cure. Changes in environment and habits, the achievement by working women of better hygienic conditions, including higher wages, and the dissemination of knowledge regarding the importance of diet in relation to health, have banished a serious form of *anaemia which caused an enormous degree of incapacity and economic inefficiency.*"

It is extremely desirable to take chlorosis out of the class of mysterious diseases and to place its etiology upon an understandable, scientific basis. It is true that chlorosis in severe form is uncommon today and is diagnosed as such very rarely. Nevertheless, a mild hypochromic anemia responding to iron occurring in adolescent girls is quite common, and severe hypochromic anemia is occasionally seen. In a routine examination of 38 presumably healthy student nurses between the ages of eighteen and twenty-three years, it was found that 26 per cent had a moderate anemia with the hemoglobin between 70 and 79 per cent. Out of 16 female technicians, aged twenty to twenty-six years, actively engaged in laboratory work, 4 showed a hemoglobin percentage slightly less than 80. Patek and Heath<sup>3</sup> have recently described 4 cases of severe iron-responding anemia in girls aged fifteen to sixteen years. The initial hemoglobin readings ranged from 29 to 44 per cent. The diet was remarkably poor in iron-containing foods in all 4 cases. In 1 case repeated nosebleeds and moderate menorrhagia were present and seemed partially responsible for the anemia. In 1 case nosebleeds alone seemed to be a factor. These cases corresponded closely to older descriptions of chlorosis. In addition to these instances there have been seen occasionally in the medical wards girls who have entered the hospital because of some infectious disease process such as lobar pneumonia, pleurisy with effusion or pulmonary tuberculosis who have shown on examination a marked hypochromic anemia which was alleviated by the administration of iron. The examination of the blood in all these instances showed

changes which were in all respects similar to those which occur in hypochromic anemia at other ages and in the male sex: the "nutritional" anemia of childhood, hypochromic anemia of blood loss, hypochromic anemia of pregnancy, and "idiopathic" hypochromic anemia.

In searching for the causes for iron-responding anemia in girls who presented no history of any great blood loss, attention was directed to the iron needs of the body and to the metabolism of iron. It was apparent from the literature that, although evidence is fragmentary and unsatisfactory, a diet restricted in iron, providing starvation does not exist, cannot result in any appreciable loss of iron from the body. In other words, a negative iron balance cannot be achieved in man by altering the diet alone when adequate calories are given. For example, Lintzel<sup>4</sup> found man in iron balance when the diet contained as little as 1 mg. of iron daily. The normal excretion of iron in the urine is practically negligible. In animal experimentation iron-responding anemia has apparently never been achieved by giving diets poor in iron, unless animals are young and growing, unless pregnancy takes place, or unless the animals are bled. It is evident, therefore, that diet poor in iron cannot be responsible alone for iron deficiency. Iron loss of some sort other than metabolic loss of iron in the urine and stools must occur. That blood loss represents a large source of iron loss is obvious since the blood is very rich in iron, containing about five times the proportion of iron of any other organ of the body under ordinary circumstances. Menstrual loss of blood, although small (averaging 50 cc. of blood each menstrual period), is constant and over many months' time represents a considerable loss, amounting on the average to nearly 1 mg. of iron a day. In pregnancy the fetus demands a certain portion of the mother's iron to supply its own body iron and iron stores. In lactation there is a certain small loss of iron equaling roughly in daily averages the amount of iron lost in normal menstruation. In growing infants and children there is a large demand for iron to supply the increasing mass of hemoglobin in the expanding blood volume.

During the first year of life the circulating hemoglobin (which embraces about four fifths of the total functioning iron of the body) approximately doubles. In effect, the growing infant "bleeds" into his own increasing blood volume. These factors, growth, pregnancy, lactation and blood loss, produce a demand for iron which must be considered first in the etiology of iron deficiency. If this demand is not met by an adequate supply of iron from the food or from medication, iron stores may become exhausted and anemia may result.

In Fig. 30 is shown the average normal annual iron requirements for males and females from birth to twenty-six years

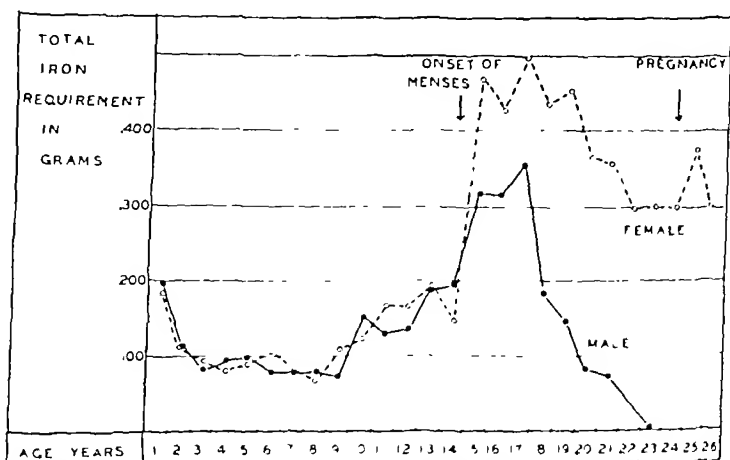


Fig. 30.—Annual physiological iron requirements for males and females, derived from figures for growth, menstruation and pregnancy.

years. Requirements for males are derived from growth statistics, for females from growth statistics together with probable losses of iron from menstruation and pregnancy. It is interesting that iron-responding anemia is seen clinically most commonly at the very times and in the same conditions that the iron demands are greatest: in infancy and early childhood after puberty, in pregnancy and in females much more commonly than in males. These iron demands must be met by adequate iron in the food, which must be absorbed through a healthy intestinal membrane, or an iron deficiency may result.

At about the time of puberty there is an acceleration of growth. This, together with the demands for menstrual loss of blood in girls, produces an annual iron requirement which is proportional to the requirement for a normal pregnancy. It is therefore quite apparent that an iron deficiency can result in girls after puberty if one of a number of factors are upset. The normal factors are: normal growth and menstruation, a healthy appetite, a good diet and a healthy gastro-intestinal tract. Abnormal factors which may condition an iron deficiency are: abnormally rapid growth, excessive menstruation or bleeding elsewhere, a diet poor in iron or poor appetite and such gastro-intestinal disorders as achlorhydria and prolonged diarrhea. The following 2 cases of iron deficiency in girls illustrate how the analysis of responsible factors can explain "chlorosis" as it is seen today, and how blood loss can easily qualify the hemoglobin level in girls after puberty.

Case I.—M. M., aged fourteen years, a white American schoolgirl, of Irish descent, was admitted to the hospital complaining of vomiting of blood. Four days before admission she went on an outing when she indiscriminately stuffed herself with a variety of food. Two days before admission she felt ill, dizzy and nauseated on rising in the morning. In the afternoon she suddenly vomited bright red blood in considerable amount, the exact amount unknown. She was put to bed and the family physician advised hospitalization.

The patient considered herself always fairly healthy. She could run, play and swim as well as other girls. However, three to five years previously she was considered underweight at school. For about four years she had mild epigastric distress and eructation of gas after each meal. One year previously, after a brief, colicky epigastric pain she visited her doctor who diagnosed her "anemic" and prescribed some iron pills. She felt improved after taking these pills. She discontinued taking them after about three months.

Two months before admission the patient had epistaxis lasting fifteen minutes, soiling five handkerchiefs. There was no other history of bleeding. She did not consistently inspect her stools but noticed no blood or tarry stools.

Menstruation began two years before admission. Periods occurred monthly with the exception of a lapse of four months, eight to four months previously. Flow persisted for five or six days. For four days 5 pads daily were saturated. Occasionally menstrual blood was clotted. Periods were accompanied by moderate pains for two days.

The patient's diet contained 1 or 2 eggs daily but somewhat reduced amounts of meat and vegetables. There was an increased ingestion of carbohydrates in the form of bread, cookies and cake. Apparently she had a good appetite, but the amount of food which she stated she consumed was perhaps

exaggerated because the cost of the diet was high and the family was poor. The approximate daily iron content of the diet was 14 mg.

*Family History.*—The father was living and well. The mother was examined briefly. She was forty-four years of age, considered herself well. She had a tendency to chronic, sore fissures at the corners of the mouth. There was slight atrophy of the tongue papillae. There was no koilonychia. She was a chronic tea drinker, consuming 7 or 8 cups a day, and a slice of bread and butter with each cup. She ate very sparingly of meat and vegetables. Her red blood cells were 5,250,000 per cubic millimeter, her hemoglobin 94 per cent. The patient's sister, aged thirteen years, was considered well but on examination showed a moderate anemia and is discussed as Case II.

*Past History.*—The patient was born and had always lived in Massachusetts. She had measles in childhood but no other diseases. A review of the cardiorespiratory, gastro-intestinal, genito-urinary and neuromuscular histories revealed nothing remarkable.

*Physical Examination.*—The patient was a pale, freckle-faced girl in no distress. The eyes, ears and nose were not remarkable. The tongue was moderately coated and not atrophic. There was no lymph node enlargement. The lungs were normal. The heart was not enlarged, the rate was regular, rapid and the sounds of good quality. There was a soft systolic murmur heard best at the apex. The blood pressure was 85 systolic, 75 diastolic. There was no tenderness of the abdomen. The liver, spleen and kidneys were not palpable. The knee and ankle jerks were equal and active. There was no pitting edema of the extremities.

*Laboratory Findings.*—The red blood cells were 2,900,000 per cubic millimeter. The hemoglobin was 54 per cent; the hematocrit was 26.7 per cent; mean corpuscular volume: 92 cu.  $\mu$ ; mean corpuscular hemoglobin concentration 31 per cent; mean corpuscular hemoglobin: 29 micromicrograms. Nine days later the red blood cells were 3,640,000 per cubic millimeter; hemoglobin 56 per cent; mean corpuscular volume 77 cu.  $\mu$ ; mean corpuscular hemoglobin 24 micromicrograms. The reticulocytes were 5.8 per cent. The icteric index was 3. The Hinton test was negative. In the blood smear the red cells showed increased variation in size and shape, moderate basophilia and many cells were small and achromic. The blood platelets were increased. The white blood cells numbered 6800 per cubic millimeter. The differential count showed polymorphonuclear neutrophils, 66 per cent; stab forms, 15 per cent; eosinophils, 1 per cent; basophils, 0.5 per cent; lymphocytes 27 per cent; monocytes, 4 per cent. The stools were guaiac positive during the first few days of entry, but subsequently were negative. Gastric analysis performed three weeks after entry showed normal acidity of the gastric contents.

Roentgen examination of the stomach with barium on two occasions revealed the presence of a small ulcer high in the lesser curvature.

*Course in the Hospital.*—The patient was given a Sippy diet with gradually increasing variety of food. After thirteen days of observation the hemoglobin remained at 54 per cent, and the reticulocytes diminished to about 1 per cent. Iron and ammonium citrate, 1 Gm. daily, was then administered. The reticulocytes increased to a peak of 6.5 per cent on the sixth day. The hemoglobin increased rapidly to 80 per cent after twenty-one days, an average



gain of about 1.2 per cent per day. No further digestive symptoms occurred. The patient was discharged with instructions to take ferrous sulphate, 12 grains daily. The hemoglobin, red blood cells and Wintrobe characteristics remained normal on subsequent visits to the hospital.

**Case II.**—A. M., aged thirteen years, schoolgirl. This girl was the younger sister of M. M., Case I. She was observed to be quite pale but claimed never to be tired or to have any symptoms of ill health. Her periods commenced six months previously. These occurred monthly, lasted four to five days, required 3 to 4 pads daily; sometimes large pads. She thought that she flowed somewhat more than her sister. Her diet was similar to that of her sister with the exception that she liked meat and ate it daily. She partook of rather excessive amounts of bread and other carbohydrate. About three years previously she had quite frequent, moderate attacks of epistaxis. For the past eight months she had epistaxis three times, requiring 2 or 3 cloths and lasting fifteen to twenty minutes. Three years previously in an accident she was said to have bled considerably from a cut on the forehead. Physical examination revealed no definite abnormalities in this girl except moderate pallor.

**Laboratory Findings.**—The red blood cells numbered 4,850,000 per cubic millimeter. The hemoglobin was 79 per cent. There were striking changes of the red cells in the blood smear; there was definitely increased variation in size, some in shape, and most of the cells were rather pale. The blood platelets and white blood cells appeared normal.

The patient was instructed to take ferrous sulphate, 4 grains twice daily. At the end of five weeks the red blood cells numbered 4,895,000 per cubic millimeter and the hemoglobin was 88 per cent. The characteristics of the red blood cells in the smear had improved greatly.

These two girls on examination both showed the characteristics of a hypochromic anemia or iron deficiency anemia, and both responded to iron medication with alleviation of the anemia. The anemia in the second patient was slight. It was more apparent on examination of the blood smear that there was abnormality of blood formation. Because the girls were sisters, nearly of age, grew at a similar rate and partook of similar diets, it is probably justifiable to assume that the blood condition of the second girl was similar to that of the first before gastric bleeding occurred. In other words, Case II serves as a control to Case I.

Annual height and weight measurements of the two girls were obtainable through the schools. The probable blood volumes per meter of body surface were estimated and from these figures the annual iron requirements for growth were

exaggerated because the cost of the diet was high and the family was poor. The approximate daily iron content of the diet was 14 mg.

*Family History.*—The father was living and well. The mother was examined briefly. She was forty-four years of age, considered herself well. She had a tendency to chronic, sore fissures at the corners of the mouth. There was slight atrophy of the tongue papillae. There was no koilonychia. She was a chronic tea drinker, consuming 7 or 8 cups a day, and a slice of bread and butter with each cup. She ate very sparingly of meat and vegetables. Her red blood cells were 5,250,000 per cubic millimeter, her hemoglobin 94 per cent. The patient's sister, aged thirteen years, was considered well but on examination showed a moderate anemia and is discussed as Case II.

*Past History.*—The patient was born and had always lived in Massachusetts. She had measles in childhood but no other diseases. A review of the cardiorespiratory, gastro-intestinal, genito-urinary and neuromuscular histories revealed nothing remarkable.

*Physical Examination.*—The patient was a pale, freckle-faced girl in no distress. The eyes, ears and nose were not remarkable. The tongue was moderately coated and not atrophic. There was no lymph node enlargement. The lungs were normal. The heart was not enlarged, the rate was regular, rapid and the sounds of good quality. There was a soft systolic murmur heard best at the apex. The blood pressure was 85 systolic, 75 diastolic. There was no tenderness of the abdomen. The liver, spleen and kidneys were not palpable. The knee and ankle jerks were equal and active. There was no pitting edema of the extremities.

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estimated. These are shown in the tabulation and compared with average iron requirements at this age. At the foot of the tabulation requirements of iron for losses of blood are also

TABSULATION			
APPROXIMATE ANNUAL IRON REQUIREMENTS FOR GROWTH AND BLOOD LOSS.			
GRAMS OF IRON			
Iron requirement for growth:			
Age, Yrs.	Case I.	Case II.	Average normal.
8- 9.....	0.15	0.09	0.11
9-10.....	0.15	0.13	0.12
10-11.....	0.18	0.15	0.16
11-12.....	0.13	0.25	0.16
12-13.....	0.19*	0.19*	0.19
13-14.....	0.12	....	0.15
Total.....	0.92	0.81	0.89
Iron requirement for:			
Menstruation.....	0.60	0.15	
Epistaxis.....	0.01	0.04	
Bleeding from wound....		0.02	
Hematemesis.....	0.50		
Total.....	2.03	1.02	0.89

\* Onset of menses (average normal age of onset is fourteen years).

given. These are estimated conservatively from the following figures: 50 cc. of blood for each menstrual period, 10 cc. of blood for each bout of epistaxis, 1160 cc. of blood for the gastric bleeding in Case I, 50 cc. of blood for the loss which occurred from the wound in Case II.

Although the iron requirements for growth in the two patients were similar to the average normal, the total iron requirements were greatly in excess because of the early onset of menses and because of pathological blood loss. In Case I the total iron requirement for growth and blood loss between the ages of twelve and fourteen years was 1.42 Gm. If spread out evenly over the course of the two years this would represent an average daily requirement of about 2 mg. of iron. Experience shows that this is a relatively large daily iron requirement. Although the daily iron of the diet of the patient was about 14 mg., only a small portion of this is available for absorption. More knowledge is necessary concerning the amount of iron retained from the food in human patients with

anemia before it can be said that a daily iron requirement of more than 1 mg. can always be met by the iron of the diet. Iron losses due to growth or bleeding exceeding 1 mg. a day are apt to result in hypochromic anemia, and this fact would lead to the belief that this is the usual limit of availability of iron from the food of the ordinary diet. Although a requirement of 2 Gm. of iron for six years, which was present in Case I, seems very small, it is large compared with the total amount of iron of the body at this age, which is about 3 to 4 Gm. Losses of nitrogen, calcium or other necessary substances involving over the course of years one half the total of the body surely might lead to deficiency syndromes unless adequately met by a suitable supply.

It is quite likely that the two patients under consideration received from their mother an inadequate store of iron at birth. We have no evidence that the mother was deficient in iron, but we do know that she subsisted on a poor diet and that she had slight atrophy of the papillae of the tongue and a tendency to sore fissures at the corners of her mouth, signs which are characteristic in "idiopathic" hypochromic anemia occurring in women of this age. It can be supposed that the daughters never built up adequate iron stores in early school years and that they entered puberty, if not anemic, at any rate without available iron stores.

The frank blood loss by hematemesis in Case I apparently takes it out of the classification of typical chlorosis. Nevertheless, hematemesis has been mentioned in the older literature as not unusual in chlorosis.<sup>5</sup> The characteristics of the anemia, the obvious iron deficiency and the improvement of the blood after iron medication are in no way different in cases of hypochromic anemia in girls having no obviously increased blood loss. Modern methods of examination enable us to locate the source of bleeding, in this case a gastric ulcer.

Since the etiology of chlorosis depends upon conditions which are universally current, such as growth, blood loss and inadequate diet, it is unlikely that the disease should completely disappear. Indeed, chlorosis has not disappeared.

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It is quite likely that the two patients under consideration received from their mother an inadequate store of iron at birth. We have no evidence that the mother was deficient in iron, but we do know that she subsisted on a poor diet and that she had slight atrophy of the papillae of the tongue and a tendency to sore fissures at the corners of her mouth, signs which are characteristic in "idiopathic" hypochromic anemia occurring in women of this age. It can be supposed that the daughters never built up adequate iron stores in early school years and that they entered puberty, if not anemic, at any rate without available iron stores.

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Since the etiology of chlorosis depends upon conditions which are universally current, such as growth, blood loss and inadequate diet, it is unlikely that the disease should completely disappear. Indeed, chlorosis has not disappeared.

That it is much less common seems not difficult to explain. In the present century girls and women in general have become emancipated to a large extent from an indoor existence. The principles of hygienic life and diet have been widely advertised and adopted. Outdoor activities are no longer taboo among young women as the general life of the two sexes has become more and more comparable. A healthy appetite usually is an effect of freedom of life and exercise and means in general a good diet.

A thorough knowledge of the causative factors of chlorosis can be helpful to the clinician in a number of ways. The presence of an iron deficiency should always be considered as a serious symptom, for although the anemia itself rarely is serious, it may indicate the presence of serious pathology. The point of view of regarding a "secondary anemia" as merely a very minor abnormality can lead an observer into very grave error. For example, "secondary anemia" may be the result of a neoplasm of the stomach which is silently bleeding. When confronted with a case of anemia in a girl and especially in a boy, the clinician should make sure, before diagnosing "secondary anemia" or chlorosis that the causes for an iron deficiency are present. "Idiopathic" cases of iron deficiency apparently do not exist. If the anemic girl gives a perfectly normal history of growth, menstruation, diet, and absence of blood loss it is extremely unlikely that one is dealing with a case of chlorosis. Other causes for anemia must be searched for, some examples being: infectious disease, such as pulmonary tuberculosis; chronic nephritis; occult bleeding from some gastrointestinal pathology; hemolytic anemia; myxedema.

The treatment of iron deficiency in girls is in no way different from the treatment of iron deficiency at other ages. Large doses of inorganic iron preparations are indicated, common preparations in use being: ferrous sulphate (daily average dose: 12 grains); iron and ammonium citrate (6 Gm. daily); reduced iron (2 to 4 Gm. daily). It is advisable to commence with small doses and gradually increase them. Medication should continue for many months after the anemia is alleviated



in order to build reserve stores of iron. It is perfectly appropriate to give small daily prophylactic doses of iron to girls at puberty, for example, 1 pill a day containing ferrous sulphate, 3 grains, or 1 level teaspoonful of iron and ammonium citrate scales dissolved in milk, daily.

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## CLINIC OF DR. LOUIS K. DIAMOND

FROM THE DEPARTMENT OF PEDIATRICS, HARVARD MEDICAL  
SCHOOL AND THE INFANTS' AND CHILDREN'S HOSPITALS

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### CONGENITAL HEMOLYTIC ANEMIA IN INFANCY AND CHILDHOOD

CONGENITAL hemolytic anemia has been recognized since its descriptions by Minkowsky<sup>1</sup> in 1900 and by Chauffard<sup>2</sup> in 1907. In an excellent review of this disease entity in 1922, Tileston<sup>3</sup> detailed the characteristics of the disturbance, the differential diagnosis, the complications and the treatment. Since then, numerous case reports and reviews have stressed the diagnostic features, especially as they occur in adults. In infancy and in childhood, however, the disease may manifest variations from the usual course. These consist chiefly of more profound anemia, cardiac enlargement and sometimes decompensation, and interference with proper skeletal growth. It is the purpose of this presentation of 6 illustrative cases chosen from a group of 20 studied here, to call particular attention to these variations in the disease as it occurs in the younger age group.

The chief characteristics by which the diagnosis is established appear equally well in congenital hemolytic anemia in infancy and in childhood. These are, a chronic or recurring type of anemia associated with relatively mild icterus becoming accentuated during crises of hemolysis; enlargement of the spleen; increase in amounts of urobilin in the urine and stools; increased fragility of the erythrocytes in hypotonic saline solutions; elevation in percentage of reticulocytes in the circulation out of proportion to the degree of anemia

present; and a tendency for the erythrocytes to be microcytic and globular.

As is true of many other diseases seen both in adult life and in infancy and childhood, these characteristics of the disease may be more marked in the young. For example, jaundice may not be as prominent a symptom, whereas the anemia may become so severe especially during crises of hemolysis that death may result from lowering of erythrocyte and hemoglobin levels and subsequent anoxemia. The well-known saying that "adults with the disease are more jaundiced than sick" should be reversed to read "children, and especially infants, with this condition are more sick than jaundiced." The spleen may become so enlarged as to fill the whole left side of the abdomen; the blood changes are generally more severe, that is, the anemia is more profound, the cells show much more tendency to variation in shape, the reticulocytes may rise to tremendous percentages, such as in one case reported from this clinic in which they numbered about 90 per cent of all the erythrocytes; and the fragility test may show hemolysis beginning in normal isotonic saline solutions. The other outstanding changes to be met with in congenital hemolytic anemia in the young will be illustrated in the cases detailed below.

**Case I.**—A four-and-one-half-month-old female infant was brought to the hospital on account of anemia of about two months' duration.

The family history showed no other instances of anemia or jaundice in any individuals related to the patient. Three other siblings were living and well. Their blood examinations as well as those of the parents offered no suggestion of a condition similar to the patient's.

The past history had been unimportant until the time of onset of the present illness. The infant had been born by normal delivery, at term; the birth weight was 8 pounds 3 ounces. She had been placed under the care of a competent physician immediately after birth and had grown and gained well. There had been no jaundice or pallor.

The present illness began at the age of two and one-half months when the parents noticed a definite pallor which gradually increased in severity during the next two weeks. At the age of four months this pallor was very marked; a determination of the blood levels at this time showed an erythrocyte count of 2,000,000 per cubic millimeter and a hemoglobin of 40 per cent. In the stained smears of the blood there appeared to be many nucleated erythrocytes. At the suggestion of the family physician, liver was given but produced

no beneficial effect. There was an increase in pallor during the two weeks before entry and slight icterus began to be visible. There was also occasional transitory feverishness. No drugs had been administered.

Physical examination revealed a well developed and nourished infant weighing 12 pounds. She was bright and alert. There was marked pallor of the skin and mucous membranes and slight icterus of the skin and sclerae. The heart was enlarged to percussion and a loud, blowing, systolic murmur could be heard over the entire precordium. The abdomen was full and distended. The spleen filled the left flank to the level of the crest of the ilium and extended to the midline as far as the umbilicus. The liver was enlarged about 4 cm. below the costal margin.

Laboratory data included: erythrocytes 1,500,000 per cubic millimeter; hemoglobin 24 per cent; uncorrected white blood count 45,000 per cubic millimeter; in the stained smears there were 40 nucleated erythrocytes per 100 nucleated cells, as well as 31 per cent reticulocytes. Many of the leukocytes were immature. The fragility of the erythrocytes in hypotonic saline solutions showed hemolysis beginning at 0.85 per cent and complete at 0.38 per cent (control 0.46 to 0.22 per cent). The van den Bergh test was indirect and showed four times normal bilirubin content. In the urine and the stools there were excessive amounts of urobilinogen. Blood cultures and stool cultures yielded no growth of pathogenic organisms. The Wassermann and tuberculin tests were negative. Roentgenograms showed a moderate enlargement of the heart but no other abnormalities. The bones seemed normal.

Course: during the first week of observation, the temperature was only occasionally elevated above 100° F. There was no evidence of acute or chronic infection or toxemia. The blood levels failed to rise in spite of the high reticulocytosis and evidences of continued increased blood destruction were present. Transfusion with matched citrated whole blood was given on two successive days and then operation performed. A very large, firm, rough-surfaced spleen, weighing 144 Gm., was removed. Further observation at the time of operation showed an enlarged but normal appearing liver and a moderate enlargement of the mesenteric lymph nodes. Following operation the convalescence was normal and a rapid improvement in blood levels occurred. Five days post-operatively, the erythrocytes numbered 2,300,000 per cubic millimeter and the hemoglobin was 36 per cent; eight days later the red blood cells numbered 4,000,000 and the hemoglobin was 59 per cent. The icterus of the skin and sclerae and bilirubinemia rapidly subsided. The infant was discharged twelve days after operation, in excellent condition. During the ensuing three years the blood levels have remained within normal limits, the patient has gained and grown in normal fashion and has had no further attacks of jaundice or pallor. The excessive fragility of the erythrocytes has slowly decreased although at the last examination the values were still somewhat above normal. Roentgenograms have shown relative decrease in the size of the heart in comparison with the chest and the cardiac murmur has disappeared.

*Comment.*—Although there was no history of the condition occurring in this patient's family, the first symptoms of

the disease were seen at the very early age of two and one-half months. The rapidity of development of the anemia was characteristic of the progress of the disease in the young infant during a hemolytic crisis.

The physical examination showed much greater pallor than jaundice; there was enlargement of the heart with loud, blowing murmurs resulting from the severe anemia; and there was great enlargement of the spleen, as well as of the liver. Nucleated erythrocytes in addition to reticulocytes were present in the circulating blood in large numbers. Because of the relatively acute course and age of the patient there had been no time for development of skeletal changes discernible by roentgenogram. Operation produced a very rapid and satisfactory improvement in the levels of erythrocytes and hemoglobin, as well as complete relief of the symptoms for which the patient had been admitted. Frequent observations during the following three years have revealed no tendency for recurrence of hemolytic crises and growth and development were normal. In summary, this represents a most satisfactory result from early diagnosis and treatment in a young infant with the disease.

**Case II.**—A six-month-old male infant was referred here by his family physician because of pallor, and an abdominal mass.

The family history was unessential. No other child had had a similar complaint. No relative had been known to have pallor or jaundice.

The past history related that the child had been born at term, weighing 8½ pounds. There had been no appreciable jaundice or pallor in the first months of life. Breast feeding had been well taken and the gain in weight had been very satisfactory.

When the infant was four and one-half months of age, the parents noticed definite pallor of his skin and mucous membranes. This had gradually increased for the following three weeks. When seen by the family physician at five and one-quarter months, there was a moderate degree of pallor and slight icterus of the skin and sclerae. In the ensuing three weeks until hospitalization occurred, the pallor became very marked, there was occasional feverishness, severe anorexia and a slow swelling of the abdomen. The icterus had faded somewhat. The stools had been noted to be a dark orange-brown in color and the urine was likewise orange colored. One day before entry, the infant's color became very "poor"; he was lethargic and refused to nurse at the breast.

Physical examination revealed a well-developed and well-nourished infant. The skin and mucous membranes were extremely pale and only slight icterus.

was visible in the sclerae. The respirations were rapid and deep. The heart was enlarged 2 cm. outside the nipple line to the left. There was a gallop rhythm, the rate was 180, and loud systolic and diastolic murmurs were heard all over the precordium. The abdomen was protuberant with a large firm splenic mass reaching to the crest of the ilium on the left and an enlarged liver extending down to the level of the umbilicus on the right.

Laboratory examinations included: a red blood count of about 1,000,000 per cubic millimeter; reticulocytes numbering about 80 per cent; many nucleated red blood cells in the stained smear; the majority of the normal erythrocytes were small globular cells, well-filled with hemoglobin. The urine was orange-colored and contained urobilin in concentrations of about one hundred times normal. A fragility test partially performed by the use of capillary blood showed hemolysis in saline solutions beginning at 0.8 per cent.

Shortly after entry, and before transfusion could be performed, the patient's respirations ceased.

*Comment.*—This infant began about the fourth month of life to develop progressive pallor and weakness. When first seen in the hospital, congenital hemolytic anemia was suggested by the course, the symptoms and characteristic blood changes. However, the anemia had progressed to so serious a degree and signs of cardiac decompensation due to anoxemia and anemia were so marked that the first efforts needed to be directed toward prolonging the life of the child by transfusion. Unfortunately, before this could be done, death occurred. This may serve to illustrate, therefore, the much smaller margin of safety which occurs in the course of hemolytic crises of congenital hemolytic anemia in infancy. Whereas it is not uncommon to wait for a recurrence of these crises in the adult before confirming the diagnosis and suggesting surgical treatment, in the infant it is advisable to perform the life-saving operation of splenectomy as soon as the diagnosis can be confirmed, even during, or immediately after, the first hemolytic crisis.

**Case III.**—A five-year-old boy was referred to the hospital by his family physician because of frequent attacks of jaundice.

The history was somewhat inaccurate because of language difficulty and lack of observation by the parents. The father had always been well but the mother was said to have been pale and frequently somewhat jaundiced from early in childhood until she had reached adult life. Since her marriage she had been moderately well and free of jaundice or definite pallor. There had been no other pregnancies.

The past history related that the child had been healthy throughout the first year of life. After that time, he had exhibited moderate pallor of the skin and mucous membranes and occasionally "looked yellow." However, he had not been taken to a physician nor been treated for this disturbance because of the mother's personal experience. The appetite had been poor especially when he was "yellow looking." At such times he frequently complained of severe abdominal pain, relieved by vomiting.

At three years of age, following an attack of measles, the patient became much more pale and jaundiced and complained of severe abdominal pain radiating from the umbilicus to the left side and accompanied by vomiting. This illness subsided after one week but left him very pale, weak and tired. From this time on, there had occurred frequent attacks of abdominal pain radiating to either side, increasing in severity, and always accompanied by feverishness, jaundice and pallor.

Seven months before entry (at the age of four and one-half years) during a recurrence of the acute attack of abdominal pain, a physician made the diagnosis of ruptured appendix with peritonitis because of the tenderness and spasm of the abdomen. A laparotomy was performed. At operation, a long, slightly reddened, and adherent appendix was removed, and it was noted that both the spleen and the liver were much enlarged and the mesenteric lymph nodes seemed much larger than usual. While in the local hospital for this surgical procedure, the patient was noted to be moderately jaundiced and the red blood count found to be 3,000,000 per cubic millimeter with hemoglobin slightly below 60 per cent. The urine was said to be normal excepting for its dark amber color.

Following operation the patient seemed slightly improved, the icterus gradually faded during the course of one month and his color became more ruddy. However, five months before entry, there was another attack of severe generalized abdominal pain lasting one week, during which his jaundice returned, his pallor increased, and the urine and stools were once more dark. Similar episodes occurred about once a month up to the time of entry.

Physical examination revealed a pale small boy with brownish yellow color to his skin and pallor of his lips and mucous membranes. There was enlargement of the heart and loud murmurs were heard all over the precordium. The liver and the spleen were enlarged to the level of the umbilicus. Laboratory examinations showed an erythrocyte level of 3,700,000 per cubic millimeter, hemoglobin 58 per cent; reticulocytes 10 per cent; white blood cells 15,000 per cubic millimeter with occasional immature cells and 2 nucleated erythrocytes per 100 leukocytes. The fragility of the erythrocytes in hypotonic saline solutions showed hemolysis beginning at 0.76 per cent and complete at 0.33 per cent. Urobilin excretion in the urine and stools was markedly increased. Roentgenograms revealed marked retardation in growth and development of the skeletal system as well as enlargement of the heart, the liver and the spleen.

During the brief stay in the hospital, the patient remained afebrile and relatively well. Operation was urged but permission was absolutely refused by the parents. Following two visits to the dispensary during which the patient's physical and laboratory findings remained essentially unchanged, the child was not seen again. Subsequent history disclosed that recurrences of



abdominal pain, jaundice and pallor continued at increasingly frequent intervals and that about one year after his last hospital visit, during one of these attacks, the child quickly failed and died.

*Comment.*—A review of this case impresses us with the frequent occurrence of severe abdominal pain accompanied often by vomiting and some fever during the hemolytic crises of the disease in childhood. Frequently the pain is associated with tenderness and rigidity of the abdomen and therefore simulates the presence of an acute surgical abdomen. The differential diagnosis of congenital hemolytic anemia from an acute surgical condition may be difficult, especially if jaundice is not too prominent and if the character of the red blood cell changes is not appreciated. In this boy's case the diagnosis of ruptured appendix with peritonitis was made and only during the operation, when the enlargement of the liver and spleen were noted, was it appreciated that some other condition might have accounted for the abdominal symptoms. Although the diagnosis of congenital hemolytic anemia was later substantiated, the previous unhappy experience with an unsuccessful operation influenced the parents against permitting another operation. The subsequent course of the patient was typical of the disease in that the attacks became more severe and more frequent and during one of these the child succumbed, presumably from the usual sequence of events: anemia, anoxemia, cardiac enlargement and decompensation. One other point of interest in this case is the presence of marked retardation in growth and development of the skeletal system which is so frequently seen in the growing child afflicted with a chronic, recurrent disease.

*Case IV.*—A two-and-eight-twelfths-year-old girl came to the hospital because of persistent pallor.

The family history was essentially negative in that neither the father, the mother nor other children, nor any relatives were suffering from a similar complaint.

The past history showed that the infant had been fairly well for the first six months of life and then had begun to "look pale." The appetite had become poor. Measles, pertussis and subsequent bronchitis before the second year had increased her usual pallor.

Following the recurrence of severe bronchitis at the age of two years, the whiteness of her skin and mucous membranes became much more marked and there was a slight degree of jaundice visible in her sclerae. This persisted until the time of her entry.

Physical examination revealed a small, poorly developed and nourished female child, whose skin was lemon yellow and whose lips and mucous membranes were blanched. She appeared somewhat drowsy and apathetic. The respirations were rapid as was the pulse. The heart was enlarged 3 cm. to the left of the nipple line; a systolic murmur could be heard all over the precordium. The spleen was moderately enlarged, about 4 fingerbreadths below the costal margin, and the liver likewise was enlarged and tender to palpation. Shifting dullness and a fluid wave were demonstrable in the abdomen.

Laboratory examinations: the erythrocyte count was 1,700,000 per cubic millimeter; the hemoglobin level 30 per cent; leukocytes numbered 9000 per cubic millimeter. Stained smears of the blood revealed small cells well-filled with hemoglobin and moderate poikilocytosis. The reticulocytes numbered 15 per cent and there were 8 nucleated erythrocytes per 100 leukocytes. Fragility of the erythrocytes in hypotonic saline solutions showed hemolysis beginning at 0.68 per cent and complete at 0.46 per cent; at a second examination, hemolysis began at 0.76 per cent and was complete at 0.46 per cent. The urine and stools showed increased amounts of urobilinogen. Roentgenograms confirmed the marked enlargement of the heart, retardation in growth and in development of the carpal centers, marked thinning of the cortices of the bones of the extremities with increased width of the medullary portions.

The patient was transfused and then sent to the Convalescent Home for the purpose of improving her nutritional state. During the two months of care there, she gained rapidly in weight and in strength. As soon as she returned home, however, another hemolytic crisis occurred, necessitating readmission to the hospital.

Following transfusion, splenectomy was performed (at the age of three years) with the removal of a large, firm spleen. There occurred an uneventful convalescence, and the patient was discharged home three weeks following operation, showing marked improvement in her general condition as well as her blood, though a slight degree of anemia still persisted.

During the ensuing nine years this child has been seen at regular intervals. She has remained constantly free of any evidence of increased hemolysis of the red blood cells, has grown and gained very well. At a recent examination, the only discernible abnormalities were a slight persistence of the tendency to increased fragility of the erythrocytes in hypotonic saline solutions (0.54 to 0.3 per cent) and slight retardation in ossification of the carpal centers (about one year below the chronological age, whereas at the time of operation they were two and one-half years below the chronological age).

*Comment.*—In this patient's illness the following details stand out particularly clearly. Besides the usual findings characteristic of the disease there was present much more than the usual evidence of interference with bodily function due to re-

current anemia. These were marked cardiac enlargement with cardiac decompensation, as evidenced by the very rapid pulse and respiration and tenderness of the liver on palpation, as well as shifting dullness in the flanks. In addition, roentgenograms showed retardation in growth and development of the carpal centers corresponding to an estimated age of one year instead of the chronological age of three years. Likewise, there was marked thinning of the cortices of the bones of the extremities with increase of the medullary portions, a picture which we have learned to recognize as characteristic of hypertrophy of the medullary substance due to chronic anemia of the congenital types<sup>4</sup> (*i. e.*, congenital hemolytic anemia, sickle-cell anemia and Mediterranean anemia of the Cooley type).

Following operation the patient made a splendid recovery and in the ensuing nine years there has been no further hemolytic crisis, although the tendency to increased fragility of the erythrocytes in hypotonic saline solutions remains. In addition the retardation in the growth and development has tended to improve, although it has not been entirely cured in this period of time. However, the bones no longer show evidence of increased medullary substances due to hyperactive, hyperplastic marrow tissue. So that in this case the operation not only controlled the tendency toward hemolytic crises but also radically changed the patient's growth and development and restored her to normal health.

Case V.—A girl, of eleven and nine-twelfths years, was brought in because of recurrent attacks of jaundice since three years of age.

Family history revealed that the father had had a mild recurrent type of jaundice since early youth but had never suffered any discomfort from this nor exhibited pallor or symptoms of anemia. Since his marriage thirteen years before, these attacks had been less frequent and his health had remained good. The two other children had no symptoms similar to the patient's.

Past history at three years of age the child had had a moderately severe attack of fever, jaundice and increasing pallor. This had lasted one week and then subsided leaving her pale and weak looking. The attacks had increased in frequency and severity from the time of onset, at first occurring about twice a year and more recently about six to eight times per year. As a consequence, she had been restricted in her activity and had been unable to attend school. The attacks started characteristically with a nonradiating, dull epigastric pain about 6 in the left upper quadrant, not colicky in type. This persisted for sev-

eral hours, to be followed by fever, then jaundice and finally pallor. Anorexia from the onset and occasional vomiting were noted. During the attacks, the stools and the urine both became dark yellow to orange in color. This color persisted for a few days and then faded. The skin discoloration usually remained for a week or two and then improved slowly.

Physical examination at entry revealed a girl, small for her age but fairly well nourished. There was a slight icterus of the skin and sclerae and pallor of the lips and mucous membranes. The heart was somewhat enlarged to the left with a loud systolic murmur best heard at the base. The spleen was palpable 4 fingerbreadths below the costal margin and the liver 3 fingerbreadths below the costal margin.

Laboratory examinations showed the erythrocyte count to be 3,200,000 per cubic millimeter; hemoglobin 10 Gm. (59 per cent); leukocytes 6800 per cubic millimeter; platelets 224,000 per cubic millimeter. Stained smears of the blood showed 7 per cent reticulocytes, small globular erythrocytes and moderate poikilocytosis. The icterus index was 40 and the van den Bergh test indirect. The fragility of the erythrocytes in hypotonic saline solutions showed hemolysis beginning at 0.85 per cent and complete at 0.38 per cent. Quantitative determinations of urobilin excretion in the urine and stools showed 3100 mg. in twenty-four hours as compared to a normal average of 80 mg. for this age.

Roentgenograms of the hands revealed a carpal development corresponding to nine years (instead of about twelve years) and general delay in bone growth. Likewise the medullary cavities of the long bones seemed increased in width.

Splenectomy was performed with relatively little difficulty. On the sixth day following this operation the platelets which had been rising slowly as is usual following this operation reached a level of 900,000 per cubic millimeter. The patient suffered an attack of severe epigastric pain necessitating morphine for its relief. This was thought to be due to mesenteric thromboses associated with the high platelet level. The following morning the platelets numbered 1,100,000 per cubic millimeter and another attack of severe epigastric pain occurred, associated with a rise in temperature to 103° F. and leukocytosis of 16,000. In the afternoon, there was a severe generalized convulsion starting on the right side and lasting several minutes. On the eighth day postoperatively the platelets were still 1,200,000 per cubic millimeter and two more severe convulsions occurred, each lasting a few minutes. Since it was felt that the high platelet level and intravascular thromboses might account for the convulsive seizures, an attempt was made to reduce the numbers of platelets by a deep x-ray treatment given over the chest to affect the largest amount of circulating blood. Following this there was only one mild attack of epigastric pain with fever and no further convulsions. On the eleventh postoperative day the platelet level was 800,000 per cubic millimeter and the following day 600,000 per cubic millimeter. At the time of discharge twenty-four days postoperatively the platelet level was 400,000 per cubic millimeter, the erythrocytes 5,400,000, hemoglobin 14 Gm. and reticulocytes 2 per cent.

The patient has had an uneventful course since discharge from the hospital one year ago, with no further changes in the blood as well as no recurrence of her previous complaints.

*Comment.*—In the family of this patient there was the suggestive history of recurrent mild jaundice suffered by the father but as so frequently occurs in adults with a mild degree of congenital hemolytic anemia, there had been very little interference with health or activity and no severe crises. In the child's case, however, the attacks had begun very early in life and had become increasingly frequent and severe from the third to the eleventh year of life. Special attention may be directed to the recurrence of deep yellow to orange urine and stool discoloration during the hemolytic crises. This has been particularly noted in children whose urobilin excretion is tremendously elevated as hemolysis occurs. In this patient about forty times the normal amounts of urobilin were being excreted by way of the urine and stools, a loss in blood pigments going hand in hand with the severity of the hemolysis and anemia which developed. Here again roentgenograms showed severe retardation in carpal development and bony growth and the long bones likewise showed expansion of the medullary substance at the expense of the cortical bone.

Following splenectomy there occurred one of the unfortunate but not rare complications of this operation. It has been pointed out by several observers that splenectomy is followed by a great rise in the levels of platelets in the peripheral circulation. Rosenthal<sup>15</sup> has followed such changes in patients with the splenic type of anemia and has related their extreme platelet elevations to the crises of fever and pain resulting from intravascular thromboses. In this child the platelets rose to over 1,000,000 per cubic millimeter at the end of the first week following operation, and severe epigastric pain, fever, and then generalized convulsions all pointed to the possibility of intravascular thrombosis associated with the very high platelet level. One method of reducing the levels of blood platelets that has been used in the past is deep x-ray therapy and in this instance such a treatment was given and was apparently effective, for the platelets fell to normal levels and remained so thereafter. The child suffered no further attacks of abdominal pain or convulsions. No method has as yet been developed

for preventing this platelet crisis following splenectomy or predicting the possibility of its occurrence. It must therefore be looked upon as a possible unfortunate complication which luckily, in our cases, has tended to be transitory and short in its duration.

**Case VI.**—An eight-year-old boy was referred to the hospital by his local physician because of recurrent attacks of feverishness followed by jaundice and pallor.

The family history was important in that the mother, a maternal uncle, and the maternal grandfather had had similar, though milder, attacks since early in life, but had never been seriously indisposed by their illness and had never required medical advice on this account.

**Past history:** in the first year of life the patient had had an attack of feverishness followed by yellowness of the skin and sclerae and moderate pallor but he had exhibited no failure of appetite nor loss of weight on this account. In his second year, the child suffered several times from "grippe" as judged by fever, abdominal pain, and vomiting, but following each such attack it was noted that he was once more jaundiced and pale and that this state lasted two to three weeks. From the third to the eighth years of life the boy had such attacks at least three to four times per year, becoming more severe and more prolonged and usually followed by anorexia and easy fatigue. Because of the increasing frequency and disability attending these attacks he had been unable to continue his schooling.

Physical examination revealed a very small underdeveloped and undernourished boy somewhat mentally apathetic. There was moderate icterus of the skin and sclerae and pallor of the mucous membranes. Small lymph nodes were palpable all over the body. The heart was enlarged 2 cm. outside the left nipple line and a loud systolic murmur was heard all over the precordium. The abdomen was protuberant with the liver palpable 4 fingerbreadths below the costal margin on the right and the spleen palpable 5 fingerbreadths below the costal margin and reaching to the umbilicus in the midline.

**Laboratory data:** red blood cells 2,600,000 per cubic millimeter; platelets 280,000 per cubic millimeter; stained smears of the blood revealed reticulocytes 22 per cent, moderate poikilocytosis, and a small globular type of erythrocyte. The icterus index was 40; fragility in hypotonic saline solutions: hemolysis beginning at 0.76 per cent and complete at 0.36 per cent. The urobilin in the urine and stools was markedly increased in quantity.

**Roentgenograms:** there was increased porosity of the bones of the extremities and the skull as well as increase in the size of the heart shadow. The carpal development was that of a child under five years (chronological age eight and one-half years).

**Course:** with all these confirmatory findings of congenital hemolytic anemia and the marked delay in development of the skeletal structures it was felt that splenectomy was definitely indicated. However, permission was refused by the parents because of their fear of any operative procedures and their feeling that the condition would improve with age as it had in the other mem-

bers of the family, suffering from the disease. The patient was therefore placed on a high iron and vitamin diet and given liver both parenterally and by mouth. There was some improvement in erythrocyte and hemoglobin levels. When seen six months after discharge from the hospital the patient related that there had been two other severe attacks of jaundice followed by pallor and extreme tiredness. Two years afterward, history revealed that the attacks were continuing unchanged in frequency or severity, necessitating one to two months' rest after each one and interfering with attendance at school. The blood showed no change from the measurements recorded at the time of hospitalization. Roentgenograms showed no development in the carpal bones and increasing porosity in the bones of the extremities and skull. In addition, the plates of the abdomen showed many small opaque bodies in the right upper quadrant, interpreted as gallstones. On careful questioning the child admitted that the abdominal pain which he frequently suffered now tended to radiate from the right side to the right scapular region and during one attack the jaundice had become much more severe than at any time previously and the stools had become clay-colored for a few days. Permission to operate was still refused by the parents.

*Comment.*—This child presents the most striking family history of any of our group of over 20 children with congenital hemolytic anemia, in that the disturbance has appeared through at least three generations, starting with his maternal grandfather. The supposition which so many laymen have that, because an adult has "outgrown" a disturbance, a child with the same disease will necessarily fare equally well is entirely erroneous and is well illustrated by the course of this boy's illness. Not only have his hemolytic crises become more frequent and more severe, but as the result of this chronic disease process his heart has become enlarged, and retardation in bone growth has occurred. The relatively infrequent childhood complication of cholelithiasis has here taken place. It is not unlikely that an attack of biliary obstruction due to gallstones will increase this child's difficulties at some future time and may make completely recovery from his disease very difficult.

#### DISCUSSION

The outstanding fact which appears from a study of these cases is that congenital hemolytic anemia which manifests its presence in childhood may not progress in as benign a fashion as it may in adult life. The younger the patient at the time

of the first crisis of hemolysis, the more severe the disturbance tends to become. Death may occur during an attack, even during the first, for the bone marrow of the young does not have as great an emergency store of erythrocytes and an hemolytic crisis may be quickly followed by all the symptoms of acute and fatal hemorrhage. The infant who is suffering from hemolytic anemia may not be able to afford to wait for a second crisis, before splenectomy need be performed.

As the child passes through succeeding attacks of hemolysis, jaundice and anemia, there appears evidence of disturbance in function of organs other than the hematopoietic-hemolytic system. The heart becomes enlarged, the valves insufficient and cardiac decompensation may occur. The growth of the skeletal structures is interfered with. Not only is stature small but the centers of ossification are delayed in appearance. In addition the bones tend to become wide but thin at the cortex. This is the result of the hypertrophy of the marrow tissue in an effort to keep up maximum erythrocyte production. In some cases there has even been a suspicion of retardation in mental development. Continued hyperbilirubinemia in unoperated cases may lead to the production of gallstones and the subsequent danger from biliary obstruction.

Early splenectomy for the infant or child with congenital hemolytic anemia is therefore indicated. Sometimes, it will be necessary as a life-saving measure. Splenectomy controls the tendency to crises of hemolysis and relieves the burden placed on the heart by the chronic and recurrently severe anemia. It likewise corrects the deranged metabolism which interferes with skeletal growth and proper bone structure.

One complication which follows splenectomy must be watched for. It consists of the building up of a tremendous platelet level within the first week or two following operation. This may be associated with evidences of intravascular thrombosis, manifesting itself in abdominal pain, fever, leukocytosis and in one of our cases, even convulsions. This "platelet crisis" usually subsides in a relatively short time.



## SUMMARY

Six cases of congenital hemolytic anemia occurring in infancy and in childhood are presented. They illustrate the variations in the disease as it manifests itself in this age group. It is emphasized that early diagnosis and prompt treatment by splenectomy are necessary since the disturbance is more acute and more severe the earlier it first appears. Death from anemia may occur in the first hemolytic crisis. Delay in treatment of the more chronic cases leads to cardiac hypertrophy and dilatation, retardation in skeletal growth and disturbance in bone structure. Likewise, cholelithiasis may develop. Splenectomy offers prompt and long-lasting relief from hemolytic crises and their attending icterus and anemia as well as from the cardiac disturbance and faulty bone growth.

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## CLINIC OF DR. ELLIOTT P. JOSLIN

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### PROTAMINE INSULIN—THE INSULIN FOR USE BY THE GENERAL PRACTITIONER FOR THE MAJORITY OF DIABETICS

PRACTICALLY all of us who have used protamine insulin have stated, and indeed, almost boasted, that we have tested protamine insulin with diabetics who were the severest of the severe and the most reliable. Perhaps this is as it should be, but the facts are that the great advantages of protamine insulin are for the many diabetics in the country and not for the few. Nobody knows how many diabetics there are in the United States or how many are mild, moderate or severe, but I suspect that there are in all between 400,000 and 500,000 individuals with diabetes, although some of them may not know they have it, that approximately 300,000 of them are mild cases, that 175,000 are moderately severe and this leaves only 25,000 who can be considered severe. Perhaps half of the mild cases can keep their diabetes controlled with a diet only moderately restricted, such as carbohydrate 150 Gm. and a reasonable amount of protein and fat, and it is because we can confidently say to the remaining 150,000 mild cases and the 175,000 moderately severe cases that their disease can be controlled with a small daily dose of this new protamine insulin and a diet which is but a whit more strict, that this great advance in diabetic therapy should be recognized and named for its discoverer, H. G. B. Zedern, M.D.

It is this factor which has raised the expectancy of the diabetic children from one year to thirty-two years and which has practically abolished coma, has more than

doubled the duration of the disease for all diabetics and, I believe, has advanced it for cases with onset in 1936 to an average duration of twenty years and quite likely twenty-five years, even though we handicap the patients under twenty years with those whose onset is above sixty years. The mere recital that in my group of diabetic doctors with onset between twenty-five and thirty-nine years the mortality is only one fourth that of my nondoctor diabetics, that only one doctor in the entire group of doctors has developed coma since 1924 and that of the doctors who have died the average age at death has been sixty-eight years, proves how much can be done in lessening mortality if the patient understands his disease. If regular insulin with its transient action has accomplished all this, how much more should be accomplished for the diabetic when under the prolonged action of protamine insulin.

Protamine insulin controls the diabetic for a whole day instead of for a six- to eight-hour period and the significance of this as yet we hardly grasp. With diabetes so much better controlled, what problems are we to meet with our diabetics in the future? Indeed, we hardly realize the possibilities for the change in the diabetic situation which protamine insulin has wrought. This was brought home to me the other day most emphatically by some figures which were placed at my disposal by Mr. Marks, working with Dr. Louis I. Dublin of the Metropolitan Life Insurance Company. I told Mr. Marks I felt sure arteriosclerosis was being deferred to some extent in our cases, because whereas Dr. Shields Warren has always found arteriosclerosis present in a diabetic of five years' duration, irrespective of age, now at autopsies this is by no means invariably true. This led Mr. Marks to compile the statistics of my own fatal cases of arteriosclerosis for two periods, and he was good enough to send me the following table (Table 1). Of course this can be improved in size numerically with time, but I think it shows quite plainly how the wind is blowing. Neither Mr. Marks nor I would claim too much for this table. We realize its deficiencies perfectly well, but it does bring out the point that the patients who die of arterio-sclero-si-

TABLE 1\*

AVERAGE AGE AT DEATH AND AVERAGE DURATION OF DIABETICS DYING FROM ARTERIOSCLEROTIC CONDITIONS† 1930-1932 AND 1933-1935 COMPARED

Site; Sex.	Average age at death.		Average duration, years.		Number of cases.	
	1930-1932	1933-1935	1930-1932	1933-1935	1930-1932	1933-1935
Arteriosclerotic conditions, total:						
Male	66 1	68.5	13.1	13.6	161	92
Female	65 7	68.5	11.4	13.1	163	123
Coronary artery disease:						
Male	64.4	67.4	13.3	15.9	53	32
Female	64 3	68.7	12.0	14.5	41	26
Gangrene:						
Male	66 9	68.7	10.8	14.6	25	12
Female	65 7	68.9	14.1	12.1	17	18

\* Prepared under the supervision of Mr. Herbert H. Marks of the Statistical Department of the Metropolitan Life Insurance Company.

† Includes deaths from chronic heart disease, cerebral hemorrhage, chronic nephritis, arteriosclerosis, gangrene, etc.

whether general or local, in the heart or legs, today are surviving diabetes for a greater number of years than before, and thus dying older, or, in other words, that the development of arteriosclerosis is being deferred. I am sure that all who look at this table can supplement it, and it is most desirable that similar data should be reported from the many diabetic clinics which exist in this country. If we can say with assurance to our patients that already with the use of regular insulin, we have seen not only complications such as coma and carbuncles reduced, but even premature old age deferred, and that now there is every reason to expect that with protamine insulin these favorable changes will be promoted, it will promote a zeal for the thorough treatment of diabetes throughout the country which is almost incalculable.

The type of protamine insulin which will go on the market (I am quite sure I am correctly informed) is protamine zinc insulin of U-40 strength. From our tests with the various

types of protamine insulin with about 700 patients, my colleagues and I can state unquestionably that protamine zinc insulin is the best we have had. Protamine insulin, fresh from Dr. Hagedorn, later from the Eli Lilly Co., and subsequently from the E. R. Squibbs and Sons Co., was a great comfort to the children in relieving them of multiple injections. Protamine calcium insulin worked still better and indeed excellently last summer with 65 girls at the Clara Barton diabetic camp. Miss Winterbottom, who has had charge of the camp for three years and thus has watched diabetic girls each summer, stated emphatically that protamine calcium insulin worked better than the regular insulin, that reactions were less frequent, that the reactions were less severe and, in general, that the children who had protamine calcium insulin wanted to continue it and the 50 or 60 who did not have it were anxious to get it. However, at our other diabetic camp, the Prendergast Preventorium, where a group of boys and girls volunteered to undergo tests with protamine calcium insulin and protamine zinc insulin, Dr. Priscilla White was able to show with the help of Dr. Schott that protamine zinc insulin was released more slowly and therefore acted a little less quickly and for a more prolonged period. Incidentally, she was able to test protamine zinc insulin produced by two of the larger pharmaceutical houses and to demonstrate that the products furnished were essentially uniform in action, which should be reassuring to all doctors.

Protamine zinc insulin will keep. I have been definitely assured that there is little if any doubt that it will last for six months with a deterioration of only 10 per cent, even though, contrary to good practice, it is not in a refrigerator all the time. Furthermore, I understand that even after the protamine has been mixed with the insulin, as in the combined preparation which is to be dispensed in a single vial, the loss of potency is not expected to be material. At this moment we are just beginning the use of this new preparation. Certainly the addition of the zinc has preserved the permanency of the flocculency of the precipitate to a remarkable degree.

Protamine zinc insulin can be used with syringes which have been sterilized with alcohol so that patients who have adopted this method of sterilization can continue it and need not change to sterilization and drying of their syringes with heat.

If regular insulin and protamine zinc insulin are given the one after the other with the same syringe, the regular insulin should be given first. Should the protamine insulin precede the regular insulin in the syringe, enough of the protamine might remain on the surface of the same to change the regular insulin to protamine insulin and thus eliminate its specific action.

The possibility for the use of protamine insulin in out-patient clinics has been emphasized by several writers, but in general its efficacy has been stressed with the responsible and pedigreed diabetic. What I want to bring out in this clinic is that protamine zinc insulin is the kind of insulin which the general practitioner and the majority of diabetics will find simplest and safest, and therefore I will report 5 cases which illustrate this one point and rest content if I make this plain.

**Case I.**—The last patient seen in the late afternoon of August 25 was a colored man, George —, 14815, thirty-four years old, with 4.2 per cent sugar, no diacetic acid. His weight had dropped from 140 to 126 pounds dressed, but physical examination presented no other striking abnormalities. I tried to get him into the hospital, but failed and so told him to take a slice of bread and an orange at each meal, and during the twenty-four hours  $\frac{1}{2}$  pint of milk and cream with a moderate amount of butter, a little cereal, four portions of 5 and 10 per cent vegetables, an egg and bacon if he could get it for breakfast, and for the other two meals a moderate quantity of meat and fish, and lastly I gave him 10 units of protamine zinc insulin. The next morning I saw him at the hospital at the Diabetic Class and he was given 10 units of protamine zinc insulin and when he returned the next day—the 27th—10 units of protamine zinc insulin and, still no hospital vacancy, I decided not to have him enter anyway, despite the fact the urine contained in 3 specimens 3.6, 2.6 and 6 per cent respectively, because I felt so much confidence that with 10 units of protamine zinc insulin the next day in one dose he would begin to clear up. And he did, because the specimens showed 4, 0.3, 0.4 and 2.8 per cent respectively. By the late afternoon of September 1, the urine contained 0.2 per cent sugar and the blood sugar was 0.12 (120 mg.) per cent. Upon September 2 the urine was sugar-free, blood sugar 0.06 (60 mg.) per cent, necessitating the reduction of insulin to 24 units, and weight 137 $\frac{1}{2}$  pounds dressed—

a gain of  $12\frac{1}{2}$  pounds in a month. Upon October 27 no glycosuria, blood sugar 0.07 (70 mg.) per cent before lunch and weight 142 pounds. And this negro did not lose a single full day's work from his job as a draftsman and in fact was only seen nine times for short visits.

I must in fairness add he was a graduate of the Massachusetts Institute of Technology.

**Case II.**—Blair W., 14484, already reported elsewhere, came to the office on the afternoon of April 9, 1936, within an hour of glycosuria having been discovered, showing 7.3 per cent urinary sugar and a blood sugar of 0.51 (510 mg.) per cent. Entering the hospital, the glycosuria was 10.4 per cent the following morning. He then was given 30 units of protamine insulin and for the next four days 50 units daily, and became sugar-free. Thereafter, for each of two days he received 46 units, the next day 40 units and was discharged with a diet of carbohydrate 210 Gm., protein 75 Gm., and fat 88 Gm. Upon May 30 he was sugar-free, taking 24 units of protamine insulin; upon July 31 he was likewise sugar-free and the blood sugar was 0.13 (130 mg.) per cent, capillary blood at three hours after lunch, with 16 units of protamine insulin daily; and upon November 15 he is still sugar-free, but requires only 8 units of protamine insulin in the twenty-four hours.

Of course, any one who has seen many cases of diabetes realizes that a child, whose treatment is begun, as in the case of Blair, shortly after the onset of the disease, will do surprisingly well. However, at the moment, I do not recall any patient whose diabetes has been as easily controlled as in this case. At no time during his illness has Blair received an injection of insulin more than once in twenty-four hours.

**Case III.**—A minister's widow, 7245, who came to me like Blair presumably within two weeks of the onset of her disease, on September 7, 1928, showing 6.9 per cent sugar and a blood sugar of 0.44 (440 mg.) per cent, did quite well with regular insulin. However, it was a bore to take 10 units of insulin in the morning and 6 units at night and so, on May 6, 1936, she was changed to 16 units of protamine insulin once daily, and I submit (Table 2) her reports sent in for the following four days, the test being made at rising, noon, afternoon and upon retiring.

Gradually reports came in at less and less frequent intervals but now are submitted once a month for analyses made on one day a week. These are also shown in Table 3.

The records of this patient not only show how much simpler modern treatment of diabetes is, but they indicate that a patient



TABLE 2.—Case III.

Mar 7		yellow	green	blue		16
8	blue	blue	blue	green		16
9	blue	green	blue	blue		16
10	blue	green	blue	blue		16

TABLE 3.—Case III.

1936	A.M.	noon	P.M.	Evening	amt.
Oct	Rising	Before Dinner	Before Supper	Before Retiring	Insulin
13	Blue	Somewhat Green	Blue	Green	14
20	Blue	Green	Somewhat Green	no test	14
27	Blue	Blue	Blue	Green	14
Nov 3	Blue	Green	Blue	Blue	14

living a reasonably uniform life can get along very well, making tests for sugar once a week.

Case IV.—Since January 24, 1931, I have taken care of Mrs. D., 9773, whose diabetes was mild, showing only 0.1 per cent sugar and a blood sugar of 618 (180 mg.) per cent upon a fairly liberal diet. Somewhat later she required 8 or 10 units of insulin once a day to control her diabetes, but in January, 1934, at the age of seventy-one years, she developed pneumonia and, despite the increasing severity of her diabetes which necessitated a total of 72

units daily administered in 6 doses, she finally recovered. Realizing the critical nature of her illness, she was treated as a surgical diabetic and given glucose and salt solution subcutaneously or intravenously so that always the carbohydrate in the diet for the twenty-four hours was at least 150 and sometimes even 200 Gm. daily. Notwithstanding troublesome diarrhea, nausea, and vomiting the disease terminated by lysis at the end of eleven days. Convalescence was uninterrupted. The following summer she journeyed to Lausanne, but the next summer she felt so sprightly that she chose Biarritz and returned taking 10 units of insulin.

By September and October, 1936, not only were two small injections daily becoming annoying, but various cardiac symptoms developed. Regular insulin was then replaced with a single dose of protamine insulin and since that time the patient has been insistent that the use of protamine insulin has relieved her of cardiac discomfort. At any rate she is much more comfortable and the diabetes is equally well, although not absolutely, controlled. The urine contained 0.2 per cent sugar and the blood sugar in the late forenoon, February 1, 1937, was 0.16 (160 mg.) per cent.

**Case V.**—Mrs. R.'s (10998) diabetes developed in April, 1932, at which time I found 3.2 per cent glycosuria and a blood sugar of 0.39 (390 mg.) per cent. She became sugar-free with insulin 12–0–12 units, eventually omitted it and was sugar-free on June 8, 1933, with a blood sugar of 0.11 (110 mg.) per cent, retaining her first weight of 153 pounds. Upon October 13, 1936, she returned with 5.4 per cent glycosuria and a blood sugar of 0.32 (320 mg.) per cent, and without insulin. She was given 20 units of protamine insulin. Upon October 17, the specimens contained 0.3 per cent sugar before breakfast and the office specimen contained 2.8 per cent sugar. Continuing on the same insulin, on October 23 the fasting specimen was sugar-free and the office specimen contained 1.8 per cent sugar, the blood sugar was 0.25 (250 mg.) per cent. One week later not only the fasting specimen was sugar-free but the single specimen contained but 0.1 per cent sugar and the blood sugar was 0.14 (140 mg.) per cent, while taking 24 units of protamine insulin.

I did not see her again until November 13 when she returned in excellent condition, urine sugar-free and capillary blood sugar 0.11 (110 mg.) per cent, at three hours after lunch, protamine insulin 20 units.

As Mrs. R. was born on October 15, 1856, her last visit was made when she was eighty years of age, thus presenting a contrast to Blair, who was eleven years old, although I might add that our youngest patient to take protamine insulin began at the age of two years.

In the last few weeks various medical societies have been kind enough to ask me to talk about protamine zinc insulin, and what has impressed me most in watching these audiences has been the change in the expression on the faces of those present when I have had a child on the platform and said to him, "George, look over these doctors and let us pretend that

this group would treat your diabetes by giving you insulin four times a day, that group three times a day, the group of doctors over there two times a day, but these doctors right here would treat you just as well as the others but would give you insulin only once a day. Which doctors in the audience, George, do you think you would like to have take care of you?" George, being a bright boy, like most diabetic boys, you cannot doubt his instant answer.



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### TREATMENT OF DIABETES MELLITUS IN THE PRESENCE OF A HIGH OR LOW THRESHOLD FOR SUGAR

#### GENERAL CONSIDERATIONS

It is generally accepted that the glomeruli of the kidney permit the passage into the tubules of a fluid, the composition of which is almost the same as that of the blood plasma except that proteins and fats normally are not allowed to pass through the renal filter. As this glomerular filtrate passes along the renal tubules, it is modified in various ways among which is the reabsorption of certain "threshold" substances of value in the body, as sugar, chloride, sodium, calcium and bicarbonate. Substances which in the normal individual are reabsorbed completely or almost completely are spoken of as possessing a high threshold. Among these is sugar, *i. e.*, glucose, for which the average threshold is often stated to be about 0.16 to 0.18 per cent. Since in normal persons the blood sugar is below this level, ordinarily all of the sugar in the glomerular filtrate is reabsorbed except for very tiny quantities of glucose excreted by some individuals along with small amounts of non-glucose reducing substances.<sup>1</sup> If the blood sugar rises above this level or if the threshold is lowered, sugar appears in the urine in quantities easily detectable by the usual copper reduction methods.

#### THE NORMAL RENAL THRESHOLD FOR SUGAR

Numerous studies have been made in order to determine the normal renal threshold for sugar and the values cited above

are merely those commonly quoted. It is generally conceded now that the renal threshold is largely an individual matter and varies widely from person to person. In interpreting the reports in the literature one must take into consideration the methods of study employed; particularly as regards—

1. The type of blood used, *i. e.*, whether arterial (capillary) or venous.

2. The blood sugar method used, with attention to the closeness with which the values obtained approach the "true sugar" content of the blood. Methods which eliminate in so far as possible nonglucose reducing substances are to be preferred.

3. The method of determining the threshold. Four methods have commonly been used:<sup>2</sup>

- (a) On different days simultaneous tests of blood and urine are made with the patient in the fasting state, hoping by this procedure to obtain some urine specimens with and some without sugar. From these data then conclusions can be drawn regarding the threshold.

- (b) A patient with glycosuria is kept in the fasting state. When frequent tests indicate that the urinary sugar is becoming slight in amount, simultaneous tests of blood and urine are made at frequent intervals until several sugar-free urine specimens have been obtained. The blood sugar value at the point of disappearance of urinary sugar is taken as the threshold figure.<sup>3</sup> One may use this method in patients with renal glycosuria and in cases with a very low threshold, a single dose of insulin may be given to reduce the blood sugar lower than could be accomplished by fasting alone.

- (c) Starting with a sugar-free urine one gives sufficient carbohydrate to cause glycosuria. At frequent intervals tests of blood and urine are made and note taken of the blood sugar level at which sugar appears in, and (on the descending limb of the curve) disappears from, the urine. Hatlehol states that Frank<sup>4</sup> was the first to note that the threshold of appearance often is not the same as the threshold of disappearance. Once glycosuria has been produced by virtue of sufficient hyper-

glycemia, the urinary sugar persists for a variable period after the blood sugar has fallen below the value initially necessary to produce glycosuria. The cause of this lag is not entirely clear. Sherrill and MacKay<sup>5</sup> consider that it is due to the "dead space" of the kidney and ureter.

The following glucose tolerance data obtained on November 16, 1936, on Mr. W. M., Case 14997, a fifty-nine-year-old Jewish clothing salesman without typical diabetic symptoms illustrate the type of response under discussion:

Time.	Urine.		Blood sugar (venous), mg. per 100 cc.
	Volume, cc.	Sugar, per cent.	
Fasting.....	50	0	0.15
100 grams of glucose by mouth			
30 minutes after glucose....	16	0.2	0.25
60 minutes after glucose....	24	3.0	0.15
120 minutes after glucose....	65	3.2	0.11
180 minutes after glucose....	80	2.4	0.08

(d) Two blood sugar curves are obtained on different days, one with an amount of carbohydrate small enough as not to provoke glycosuria and the other sufficiently large as to cause urinary sugar to appear. Blood sugar estimations as often as every five minutes are desirable and tests of the urine are made at ten- to twenty-minute intervals. The renal threshold for sugar is known to lie between the highest points on the two curves. More than two curves may be necessary to determine the threshold with accuracy.<sup>6</sup>

It has not seemed profitable to attempt a complete review of the literature concerning the average normal threshold. From a glance at Table 1 in which are summarized the results of 10 investigations, it will be readily seen that a wide range of values (0.05 to 0.39 per cent) has been reported. It is doubtful, however, if all of the subjects used could be classed as truly normal.

TABLE 1

SUMMARY OF VALUES REPORTED FOR THE RENAL THRESHOLD FOR SUGAR  
IN NORMAL INDIVIDUALS

Author.	Year.	Number of subjects.	Type of blood.	Blood sugar method.	Range of values, per cent.
Jacobsen <sup>7</sup> .....	1913	16	Capillary.	Bang.	0.17-0.18
Hamman and Hirschman <sup>8</sup> .	1917	6	Venous.	Lewis-Benedict.	0.12-0.18
Goto and Kuno <sup>9</sup> .....	1921	12	Venous (plasma).	Meyers-Bailey.	0.12-0.18
John <sup>10</sup> .....	1922	35 (nondiabetics)	Venous.	Myer-Benedict.	0.05-0.23
Höst <sup>11</sup> .....	1923	25	Capillary.	Hagedorn-Jensen.	0.11-0.22
MacKay <sup>12</sup> .....	1927	44	Not stated.	Not stated.	below 0.13- above 0.39
Glassberg <sup>13</sup> .....	1931	51 (nondiabetics)	Capillary.	Somogyi.	below 0.10- above 0.25
Himsworth <sup>14</sup> .....	1931	11	Capillary.	MacLean.	0.13-0.25
Campbell, Osgood and Haskins <sup>15</sup> .....	1932	24	Venous.	Somogyi-Shaffer-Hartman.	0.10-0.23
Sherrill and MacKay <sup>16</sup> ....	1935	11	Capillary.	Somogyi-Shaffer-Hartman.	0.08-0.16

\*In all of the studies to which reference is made in Table 1, the method employed was that outlined above under the heading (c) except in the studies of MacKay in which the blood and urine were examined before, during and after surgical anesthesia. Goto and Kuno, John, Höst (in most of his experiments), and Glassberg took as the threshold the level of blood sugar at which sugar first appeared in the urine; Hamman and Hirschman considered not only the level of appearance of glycosuria but also that of disappearance; Campbell, Osgood and Haskins noted the level of blood sugar at the time of disappearance of urinary sugar; Sherrill and MacKay did likewise except that they gave glucose intravenously rather than orally as did all other workers (except Höst in certain studies) mentioned. John's<sup>16</sup> larger series of 833 renal threshold estimations is not included because it is difficult to decide how many of his subjects can be classed as "normal." He concluded that the actual average renal threshold was "somewhere near 150 mgm."



Various factors may influence the renal threshold aside from the wide individual variation described above. Among these is the age of the individual: John<sup>16</sup> found the average threshold among 33 patients under twenty years of age to be relatively high, 174 mg. Conditions of impaired renal function may raise it; it may be elevated in nephritis<sup>8</sup> and furthermore in the carrying out of tests on individuals, normal or otherwise, the degree of renal activity as reflected in the output of urine may greatly influence the results.<sup>5</sup> It may be elevated in poisoning with certain narcotics as morphine<sup>17</sup> and in certain disease conditions as hypertension, syphilis, obesity, acromegaly, and particularly arthritis and diabetes.<sup>16</sup> It may be lowered in pregnancy or poisoning with phloridzin<sup>18</sup> or certain metals.<sup>4</sup> It is low in the condition known as renal glycosuria which undoubtedly is simply the reflection of a very low threshold.

Major<sup>19</sup> in a study of diabetic patients with hyperglycemia but without glycosuria found that the high values for blood sugar were due to a fermentable sugar, presumably glucose, and not to any nonexcretable substance.

Faber<sup>20</sup> believes that the renal threshold is constant for any individual throughout life. Other investigators, as Glassberg,<sup>13</sup> however, have reported cases in which the threshold seemed to vary from time to time. Robinson and coworkers<sup>21</sup> from studies involving the giving of 7.5 to 20 Gm. of glucose intravenously, found that the level of appearance of sugar in the urine was constant for an individual when the same dose was given but varied with different people. With the same person it varied with the dose. They suggest that in cases of hyperglycemic glycosuria "some element in the phosphorylation mechanism, such as the store of phosphate or of enzyme in the tubular membranes," becomes exhausted.

#### RENAL THRESHOLD IN DIABETES

Thirty years ago Liefmann and Stern<sup>22</sup> from a study of 8 cases concluded that the renal threshold tends to be low in cases of diabetes with recent onset and to rise as the disease

progresses. A somewhat similar view was held by von Noorden<sup>23</sup> (particularly in cases of diabetes complicated by nephritis and hypertension), by Williams and Humphreys<sup>24</sup> and by Allen and Wishart<sup>17</sup> (from dogs with experimental diabetes). On the other hand, in a study of 11 patients Hamman and Hirschman<sup>8</sup> found, on the average, higher threshold values in cases of mild, as compared with those of advanced, diabetes. Likewise, Petré<sup>25</sup> reported that the highest values were obtained among the youngest patients and among those with diabetes of recent onset. As opposed to these conflicting reports, other workers have stated that, as with normal individuals, the renal threshold in diabetic patients is an individual matter, varying from person to person, and is not related to the age or sex of the patient, the duration of the diabetes, or the severity of the disease. This was the conclusion of Jacobsen,<sup>7</sup> Faber and Norgaard,<sup>3</sup> Faber and Hansen,<sup>20</sup> Hatlehol<sup>2</sup> and Sakaguchi *et al.*<sup>27</sup> In their recent careful study Sherrill and MacKay<sup>7</sup> found an average value of 149 mg. per cent for their diabetic group as compared with that of 128 mg. for the nondiabetic group (capillary blood, Somogyi-Shaffer-Hartman method). This tendency to a higher threshold in diabetes was found also by John<sup>10</sup> who reported that among 54 diabetics the average renal threshold was at 217 mg. per 100 cc. (venous blood; Myer-Benedict method). Thresholds below 180 mg. were found in 27.7 per cent of cases and above 180 mg. in 72.2 per cent. Among 833 patients of various types, only in arthritis and diabetes was the average threshold higher than the commonly quoted value of 180 mg.

On the whole the available data seem to indicate that the renal threshold tends to be higher in diabetic persons than in normal individuals but that in both groups it varies widely and is an individual matter.

#### TREATMENT OF DIABETES IN THE PRESENCE OF A HIGH THRESHOLD

Leaving aside the question as to basis or cause, it is a fact that one not infrequently encounters diabetic patients, usually

middle-aged or elderly persons, who possess a high renal threshold (0.20 per cent or above) for sugar. Often these patients have considerable generalized arteriosclerosis with or without hypertension and often have some degree of chronic nephritis. The question then arises: should an attempt be made by giving insulin (or more insulin) to lower the blood sugar below the level at which glycosuria entirely disappears? Or should one be content with a sugar-free urine, regardless of the level of the blood sugar?

Using regular, quickly acting insulin, the attempt to maintain a normal or nearly normal blood sugar in such patients has certain drawbacks: (1) these patients are usually insulin-insensitive and sizable doses are often required to accomplish the desired effect; (2) without blood sugar determinations at intervals, it is difficult—with improvement in the condition of the patient—to foresee overdosage and consequent hypoglycemia with its deleterious action in a patient perhaps with coronary sclerosis; (3) usually little or no immediate subjective improvement is noted and one wonders whether the inconvenience and expense of daily hypodermic injections are worth while.

Because of these considerations, in our practice we have in the past ordinarily not insisted upon the use of insulin or extra insulin in patients of this type provided the urine was untotally sugar-free and no demonstrable acidosis was present. This was not, however, because of any belief that the hyperglycemia was beneficial. Now that protamine insulin has made treatment so convenient and so safe, we are beginning to use it more and more in such patients in an attempt to keep the blood sugar throughout the entire day within relatively normal limits (below 2 per cent). We have observed no ill effects from establishing a lower average glycemic level and it seems probable that any tendency to acidosis should be avoided. It is surprising how large doses of protamine insulin can be given to these elderly patients with no sign of toxicity. Thus Mrs. J. P. Case 14,375, aged fifty-eight years, has been on this treatment for months' duration, was essentially sugar-

free both with and without 40 units of protamine insulin daily. On admission to the hospital on December 29, 1935, with a deep infection of the right foot her urine had contained 2.4 per cent sugar and the blood sugar at 8:30 P. M. was 0.27 per cent. See Table 2 for relevant data.

TABLE 2

MRS. J. P., CASE 14,375, URINE AND BLOOD FINDINGS WITH AND WITHOUT INSULIN. DIET THROUGHOUT CONSISTED OF CARBOHYDRATE 140 GM., PROTEIN 60 GM., FAT 75 GM., 1475 CALORIES DAILY

Date 1936.	Urine—24-hr. amt.			Blood sugar, per cent.			Protamine insulin units per day.	Remarks.
	Vol. cc.	Diacetic acid.	Sugar total amt., Gm.	Fasting. Venous.	11 A.M. Capillary.	4 P. M. Capillary.	1 hr. after supper. Venous.	
Jan. 20-21	1250	0	11		0.25	0.32		Incision and drainage of foot, Jan. 17, 1936.
21-22	1300	0	8	0.26				
Feb. 13-14	900	0	trace	0.15	0.15	0.21		Second incision and drainage of foot, Jan 28, 1936.
14-15	1300	0	0					
Feb. 27-28	1000	0	0					Foot doing well.
28-29	700	0	1	0.15			0.22	
March 4- 5	900	0	1				0.22	Foot doing well
5- 6	1200	0	trace	0.15				

\* Regular insulin.

† Includes 20 units regular insulin.

It is a well-recognized clinical fact that patients with impairment of kidney function, particularly those with uremia or "renal block," may exhibit a raising of the renal threshold for sugar. The 3 cases of nephritis studied by Hamman and Hirschman<sup>8</sup> had threshold values higher than the general average. John's<sup>16</sup> series included no nephritics classified as such but it is interesting to note that of 49 cases with hypertension, the average threshold was 165 which is considerably above the figure of 149 for the entire group studied. Below are given in abstract form data regarding such a patient.

Mrs. L. M. S., Case 6082, fifty-one years old, with diabetes of four years' duration, was admitted to the New England Deaconess Hospital on May 16.

1927, in diabetic coma. There was infection and gangrene of the left foot with lymphangitis extending one third of the way to the knee. There was, however, on admission little or no fever. In Table 3 are listed the findings as regards the blood and urine.

TABLE 3

MRS. L. M. S., CASE 6082, MARKED ELEVATION OF THE RENAL THRESHOLD

Date 1927, May.	Urine.				Blood.				Remarks.
	Hour.	Volume, cc.	Diacetic acid.	Sugar, per cent.	Hour.	Nonprotein nitrogen.	Sugar.	CO <sub>2</sub> combining power.	
16-17	3-6.30 P. M.	90  645	0	0	5 P. M.	154	0.49	13	60 units of insulin given from 8 P. M. until midnight.
	7.30 P. M.		0	trace	8 P. M.		0.57	13	
	10.45 P. M.		0	trace	11 P. M.		0.44	13	
	1 A. M.		0	0					
	3 A. M.		0	0					
	5 A. M.		0	0					
17-18	2 P. M.	1500	0	0	8 A. M.	145	0.28	20	15 units of insulin given at 8.15 P. M. Blood pressure 106/80. Plasma NaCl 595 mg. per 100 cc.
	4 P. M.		0	0	11 A. M.		0.24	20	
	8.15 P. M.		0	0	8.15 P. M.		0.36	25	
	11 P. M.		0	0	11 P. M.		0.33	16	
	2 A. M.		0	0					
	5 A. M.		0	0					
	24-hr. amt.		0	0					
			0	0					

This patient was in the hospital for approximately a month and during most of this time had marked fever despite the fact that a guillotine amputation through the left lower leg on the day after admission removed the infected foot. The blood nonprotein nitrogen fell but never to below 65 mg. per 100 cc. She died on June 18, 1927, and at autopsy an empyema on the left and an abscess of the anterior mediastinum were found. The kidneys showed "early vascular nephritis."

Treatment in such acute cases is obviously difficult. One's chief efforts should be directed to measures designed to relieve the kidney failure with parenteral fluid, glucose and other treatment indicated, because, lacking in this, control of the blood sugar will be of no avail. However, a conscientious attempt should be made to keep the blood sugar within satisfactory limits (below 0.20 per cent). To do this, frequent determinations of the blood sugar, at intervals of two to four hours, are necessary since obviously tests of the urine, if obtained, are of no assistance. Large doses of insulin may be

necessary and may be given according to some such outline as that below:

1. Determine (capillary) blood sugar every four hours.
2. If blood sugar 0.50 or above, give 50 units.  
0.40 or above, give 40 units.  
0.30 or above, give 30 units.  
0.20 or above, give 20 units.  
below 0.20, give no insulin.

Such a schedule will, of course, vary from patient to patient but may serve as a type. As one learns more about its use, it is likely that large doses of protamine insulin may be valuable in this situation.

The cause of the elevated renal threshold in such cases is not understood but probably lies in some damage to the renal filter resulting in decreased activity with lessened volume of glomerular filtrate. The high blood sugar values obtained may be due in small part to the reducing effect on copper solutions of the large amount of nonprotein nitrogen substances in the blood, but this is not a large factor.

Before leaving the subject of the high renal threshold, it may be well to point out that if one insists, and rightly so, upon the presence of sugar in the urine in order to make the diagnosis of diabetes, then in certain individuals without glycosuria a definitely elevated blood sugar, and hence a high renal threshold, may not signify diabetes. In some patients with arthritis, for example, Nissen<sup>28</sup> has shown that definitely abnormal sugar tolerance curves—with little or no glycosuria—may be obtained despite the entire lack of symptoms or signs of diabetes or a progression toward it over a period of years.

#### TREATMENT OF DIABETES IN THE PRESENCE OF A LOW RENAL THRESHOLD

With certain diabetic patients as with normal individuals the renal threshold for sugar is low.<sup>29</sup> Such a patient is Case 8471, Miss J. E. C., aged forty-nine years, with diabetes of ten years' duration. Her renal threshold for sugar has not been accurately determined, but as Table 4 indicates, it is so

TABLE 4

MISS J. E. C., CASE 8471, DIABETES IN A PATIENT WITH A LOW RENAL THRESHOLD. THE DIET THROUGHOUT CONSISTED OF CARBOHYDRATE 166 GM., PROTEIN 90 GM., FAT 88-123 GM. DAILY

Date 1935.	Urine—24-hr. amount specimen.				Blood sugar, per cent.	Insulin.	
	Vol. cc.	Diacetic acid.	Sugar, per cent.	Total Gm.		Units.	Time.
Mar. 24	2000	0	0.8	16	0.11 10.30 A. M.	12 10	6.30 A. M. 4.30 P. M.
Mar. 25	1600	0	0.9	16	0.08 4.00 P. M.	12 6 12	6.30 A. M. 11.30 A. M. 4.30 P. M.
Mar. 26	2300	0	0.7	16	0.07 4.00 P. M.	12 12 12	6.30 A. M. 11.30 A. M. 4.30 P. M.
Mar. 27	2700	0	0.7	19	0.09 Fasting 0.07 4.00 P. M.	14 10 14	6.30 A. M. 11.30 A. M. 4.30 P. M.

low that if the insulin dosage is increased in an attempt to secure a sugar-free urine, hypoglycemic attacks occur in the presence of glycosuria. Obviously the sensible plan of treatment in such a patient is to allow a basic amount of glycosuria, as evidenced, say, by a green test with Benedict's solution.

Pregnancy lowers the renal threshold in the diabetic as well as in the normal person. This becomes manifest in the third trimester principally and the sugar excreted during this period is almost entirely true glucose. Treatment must be planned so as to allow slight glycosuria in order to avoid hypoglycemic attacks. Frequent blood sugar estimations are desirable, if not imperative, in order to direct treatment intelligently. Following delivery or the termination of the pregnancy, the renal threshold characteristic for that individual is resumed.

An important practical point in the care of any patient with glycosuria is the establishing of the correct diagnosis by blood sugar determinations or by a formal glucose tolerance test, if necessary. Otherwise diabetic treatment with diet and perhaps insulin may be imposed on an individual who because of a low renal threshold has a benign glycosuria. The following is a case in point:

Miss H. O., Case 4534, Jewish, was brought for treatment on April 6, 1925, being at that time three and one-half years of age. Sugar had been found in her urine on March 15, 1925, following an attack of tonsillitis during which her temperature had risen as high as 104° F. She spent three weeks at the New England Deaconess Hospital at that time. The admission specimen of urine contained 3 per cent sugar and subsequent daily analyses of the twenty-four-hour amount specimens showed constantly small amounts of sugar which became less, but never entirely disappeared, on treatment with diet and small doses of insulin. Because of her age, no blood sugar estimations were made; at this time capillary blood sugar estimations were not in general use.

Her parents were faithful in treatment and followed carefully the directions as to the restricted diet and insulin. She did well and in May, 1926, at the time of a tonsillectomy was excreting from 1 to 8 Gm. of sugar in twenty-four hours while receiving a diet of carbohydrate 52 Gm., protein 42 Gm. and fat 63 Gm. and from 8 to 18 units of insulin a day. Three capillary blood sugar values at this time were 0.07, 0.08 and 0.08 per cent respectively. On July 20, 1927, a capillary blood sugar of 0.21 per cent at 2 P. M. was recorded and at the time seemed to fit in with the diagnosis of diabetes. Study of her record in retrospect, however, shows this postprandial value to be the highest ever obtained in the eleven years of observation.

When seen in April, 1934, it was noted that on a diet which totaled as much as carbohydrate 194 Gm., protein 74 Gm. and fat 56 Gm. and with 10 units of insulin twice daily, all blood sugar values, either before or after meals, were normal. Furthermore on a "house diet" with sugar, glycosuria was no more pronounced even though insulin was entirely omitted. Consequently a formal sugar tolerance test using 75 Gm. of sucrose by mouth was carried out which yielded normal blood sugar values despite constant glycosuria throughout the test. The diagnosis of renal glycosuria was made. Insulin was discontinued and strict dietary treatment no longer advised. To date the patient has remained well and is developing normally.

Fortunately this patient suffered no permanent injury because of the enforcing of the diabetic regimen for eleven years. She grew satisfactorily and is in good health. However, much inconvenience was caused to her and her parents and the case serves well to illustrate the importance of careful blood studies in all patients and particularly in those in whom glycosuria persists despite normal values for blood sugar as obtained on random specimens.

### COMMENT

Experience teaches that most of the cases of diabetes reputed to be extraordinary in this or that respect, turn out on closer study to be straightforward in their course. Often laboratory errors have contributed to the confusion or correlation has been attempted between urine voided at one time and blood withdrawn hours or even days before or after. It is surprising how often hospitalization for a few days with opportunity for careful study as to complications, for con-



trolled conditions as to diet, insulin and activity and for supervision of laboratory work will clear up a confusing and supposedly unusual situation. The treatment of diabetes in the presence of a high or low threshold is usually not difficult if the patient has been carefully studied and a course of procedure well planned.

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### TRAUMA, PHYSICAL AND PSYCHIC, IN RELATION TO DIABETES

**Introduction.**—The relationship of trauma to diabetes, either as a cause of diabetes, or as a complication of existing diabetes, has long been a matter not merely of discussion but of real clinical and scientific importance. In recent years the frequency of accident insurance policies among the population of the United States and the increasing tendency to utilize the courts have resulted in the question being raised more and more frequently before judge and jury.

**Definition.**—Ordinarily, by trauma we mean a physical injury or wound produced by contact with some external object or objects. It may be accidental, unexpected, or a usual accompaniment of the activity of the subject, as in warfare. Psychic trauma is "an emotional shock that makes a lasting impression upon the mind, especially the subconscious mind" (Dorland). Trauma may be mild or severe. It may be sudden and of short duration, or of gradual onset and long duration. The effects of trauma may be direct or indirect. Thus, as a result of an injury which requires the patient to remain in bed for a long period, disturbance of the usual habits of living, including even the diet and the daily exercise, occurs. Infections at the site of trauma may introduce a totally unexpected and important factor.

**Nature of Diabetes.**—In considering the etiologic relationship of trauma to diabetes, one must bear in mind the great

frequency and universal character of diabetes. It is not merely the fact that there are in the population today 500,000 persons with diabetes in this country, and that another 2,500,000 will develop diabetes before they die, but that in all probability one fourth of the population are carriers of the tendency to diabetes which they may transmit to their own offspring. We have no way at present of selecting those destined to become the diabetics of tomorrow and the next year. In this large number the vast majority develop diabetes not at or near the time of trauma of any sort, but characteristically develop it at a time of unusually good health. The adults state usually that their weight was at maximum. The mothers of the children state usually that the child was never better than when the characteristic polyuria and polydipsia began to appear. The common precipitating factors in diabetes are well known. In adult life, obesity immediately precedes the onset of diabetes in fully 75 per cent of the cases; and this obesity frequently follows a period of months or years, in which time the habits of living have been changed notably by the reduction of the amount of muscular exercise. The pathology of diabetes is well known. Only a single method has been found so far by which diabetes can be constantly produced and that is by injury or removal of the pancreas. Pathologic observations from the time of Cawley to the present have clearly shown that the pathology of diabetes centers in the pancreas. It is true that the brilliant discovery by Claude Bernard in 1849, that glycosuria could be produced by puncture with a needle of the floor of the fourth ventricle, diverted the attention of the scientific world from the pancreas and has left as a direct result the impression that a direct part is played by some lesion in the brain upon the etiology of diabetes. Physiologic experimentation shows clearly that there is a direct innervation of the pancreas with connection to the brain and notably through the hypothalamus. Houssay abated the severity of diabetes in the depancreatized dog by removing the pituitary and Long showed that in the cat this effect depended upon the adrenal glands.

The relations of the nuclei at the base of the brain and of the higher centers to the carbohydrate metabolism are being carefully studied. It is becoming more and more clear that certain groups of cells in the central gray matter along the sylvian aqueduct and in the hypothalamus are important regulators of the autonomic nervous system, as pointed out in the review by J. C. White.<sup>1</sup> Davis, Cleveland, and Ingram<sup>2</sup> have emphasized the close relation between the hypothalamus and the pituitary. It is very difficult to tell which functions belong to the one or to the other. However, with the Horsley-Clarke stereotaxic instrument they were able to place accurate lesions in the hypothalamus and they found that under these circumstances complete removal of the pancreas was no longer followed by diabetes mellitus. The effect then was practically the same as if the pituitary had been removed as Houssay had done. Thus, when this pathway had been cut, stimulation of the superior cervical sympathetic ganglia no longer will produce hyperglycemia and glycosuria. It, therefore, appears that the hypothalamus exerts nervous control over the anterior lobe of the pituitary which may be quite important in the regulation of the carbohydrate metabolism. That the level of the blood sugar exerts the controlling influence upon the activity of the islands of Langerhans, however, seems generally agreed. It is a long leap from temporary glycosuria produced by trauma of the brain to clinical diabetes with its manifold variations, and its many complications.

**Degree of Trauma.**—In order that the trauma shall cause diabetes it must result in very grave damage to the pancreas. The severity of the damage may be judged by the fact that experimentally one can remove certainly three fourths and sometimes nine tenths of the pancreas without diabetes resulting. Ordinarily, a trauma so severe as to cause such an injury to the pancreas would be likely to cause death itself. Only rare cases may be found in literature which fulfill these requirements. It should theoretically be certain that the patient did not have diabetes before the accident occurred. If this proof were to be scientifically accurate, it should consist not

merely of an urine test made recently, but actually blood sugar analyses and even a glucose tolerance test done within an hour of the accident!!

A teamster, thirty-two years old, described by Professor H. Gideon Wells in 1922, fell from his wagon while intoxicated, and the wheels passed over his body. At the hospital 4 fractured ribs on the left side with subcutaneous emphysema were found. In twelve days he left the hospital in apparently good condition. However, he returned in four months with the history from his family that shortly after his discharge he had developed certain mental symptoms, great thirst, pruritus, jacksonian epilepsy and progressive loss of weight. He had become irritable, forgetful, and stupid. He died in status epilepticus within forty-eight hours and the bladder urine contained 2.5 per cent sugar. A postmortem examination showed an anemic infarct of three fourths of the spleen and the entire right kidney. The pancreas itself was hard and irregular and upon opening it was found to contain many deposits of calcium throughout the pancreatic tissue. These deposits of calcium were not calculi located within the ducts of the pancreas, but calcareous deposits throughout the gland itself. The gland tissue was largely replaced by fibrous tissue and there were scarcely any normal islands of Langerhans remaining. Dr. Wells analyzed the material, finding it was chiefly calcium carbonate and phosphate. In addition, he had tuberculosis of the lungs and an area of infarction and softening of the ascending parietal and frontal convolutions of the brain, evidently the result of an embolism or thrombosis.

Trauma of various sorts is almost of daily occurrence. Trauma is involved in the many dental extractions, and all the operations carried out in the hospitals. None are regarded by either patient or physician as likely to have any bearing upon the production of diabetes. Trauma, in order to cause diabetes, must be direct and produce serious injury to the pancreas. Conceivably, trauma might have an indirect effect, especially upon patients already susceptible to the development of diabetes by reason of inheritance. Thus, an accident

leading to a long continuing infection, such as osteomyelitis, with recurrences over a period of time, might by producing invalidism and overnutrition act as a precipitating cause. If the patient happened to have a diabetic heredity, then one might possibly hold that the diabetes resulting after such a long period of recurring infections, might have taken place a few months or a few years earlier than would otherwise have occurred. It must be remembered that even such gross lesions of the pancreas as acute pancreatitis and pancreatic carcinoma, usually do not cause diabetes because they do not involve a sufficiently large part of the pancreas.

**Psychic Trauma.**—We consider trauma of the central nervous system to include the tremendous number of injuries of the brain from flying shells and shrapnel, as well as the psychic trauma to which millions of men were subjected during the World War. Students of diabetes in Germany, France, England and in this country all agreed that there was no increase in diabetes produced by brain injuries or by the striking trauma of the World War. In the words of von Noorden, "the World War put neurogenic diabetes in its grave."

Yet, the opinion is still occasionally expressed that nervous wear and tear, emotional shock, and psychic trauma may be the cause of diabetes. Occasionally, a striking case may occur, such as the following:

Case 14,050, aged thirty-three years, gave the following history: six or eight weeks previously, because of a slight automobile accident, he had consulted a doctor who found the urine to be sugar-free. One month before the day of his examination, his weight was 210 pounds dressed, which was the highest weight he had ever had. There was no known history of diabetes in the family. His occupation was that of a labor representative, which meant that in contrast to his former activity, he was now in an executive position.

Twelve days before he was driving his own car along one of the main automobile thoroughfares leading out of Boston and had some personal friends in the car. Suddenly, a wheel came off and as he looked ahead he saw a train of large trucks approaching him so that for the moment he realized the great danger and that he might not be able to prevent his car from being run into the trucks, or else going over to the other side into the ditch. In his own words he "saw death staring him in the face." However, somewhat to his surprise he stopped the car without any accident occurring, so that there was no actual physical trauma whatever. As he walked along the street

merely of an urine test made recently, but actually blood sugar analyses and even a glucose tolerance test done within an hour of the accident!!

A teamster, thirty-two years old, described by Professor H. Gideon Wells in 1922, fell from his wagon while intoxicated, and the wheels passed over his body. At the hospital 4 fractured ribs on the left side with subcutaneous emphysema were found. In twelve days he left the hospital in apparently good condition. However, he returned in four months with the history from his family that shortly after his discharge he had developed certain mental symptoms, great thirst, pruritus, jacksonian epilepsy and progressive loss of weight. He had become irritable, forgetful, and stupid. He died in status epilepticus within forty-eight hours and the bladder urine contained 2.5 per cent sugar. A postmortem examination showed an anemic infarct of three fourths of the spleen and the entire right kidney. The pancreas itself was hard and irregular and upon opening it was found to contain many deposits of calcium throughout the pancreatic tissue. These deposits of calcium were not calculi located within the ducts of the pancreas, but calcareous deposits throughout the gland itself. The gland tissue was largely replaced by fibrous tissue and there were scarcely any normal islands of Langerhans remaining. Dr. Wells analyzed the material, finding it was chiefly calcium carbonate and phosphate. In addition, he had tuberculosis of the lungs and an area of infarction and softening of the ascending parietal and frontal convolutions of the brain, evidently the result of an embolism or thrombosis.

Trauma of various sorts is almost of daily occurrence. Trauma is involved in the many dental extractions, and all the operations carried out in the hospitals. None are regarded by either patient or physician as likely to have any bearing upon the production of diabetes. Trauma, in order to cause diabetes, must be direct and produce serious injury to the pancreas. Conceivably, trauma might have an indirect effect, especially upon patients already susceptible to the development of diabetes by reason of inheritance. Thus, an accident



however, did not seem serious enough to interfere with her housework, so she continued all that day. The next day the knee pained her severely requiring morphine for relief and the knee continued to be painful and became swollen. On December 20, she was brought into the hospital in profound diabetic coma, with plasma  $\text{CO}_2$  of 17 volumes per cent and blood sugar of 0.42 (420 mg) per cent. She required 210 units of insulin in the first ten hours in the hospital, and emerged from coma. During the next few days, however, she continued to have a slight fever for which we could not find an explanation. The knee was swollen without any break in the skin and it seemed to be due merely to an accumulation of noninfected fluid in the joint. Incidentally, under a callus on one toe of the same leg an area of infection was found, which apparently had been there for a long period of time. She continued to go down hill, became septic and a roentgenogram showed gas in the right knee joint and also extending up the thigh along the fascia. The infected areas were deeply incised for drainage but she died following a hemorrhage from a duodenal ulcer. At postmortem examination it was clear that she had a streptococcus infection of the knee joint which had broken through the joint capsule and had extended up the thigh along the fascial planes and that she died of the combination of infection and a large hemorrhage from an old duodenal ulcer.

The source of the streptococcus infection is unexplained unless the following course of events be accepted. She had a local infection in the toe of the right foot under the callus. As a result of the fall and trauma to the knee, together with the development of acidosis, the resistance to infection was diminished and the organisms escaped from the toe to lodge in the knee at the point of lowered resistance. Again, partly due to the fact that her resistance was diminished by the acidosis, the infection was able to break through the joint capsule, an uncommon event in even a diabetic, and extended up the thigh.

This case then illustrates:

1. The extreme importance of clearing up small focal infections.
2. The direct and remote dangers of trauma in diabetic patients, the always present threat of acidosis with the complications which it may bring about.
3. A latent but serious disease which, quite apart from the trauma, could have been a cause of death.

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toward a garage some distance away, hoping to get help, he noticed that his mouth was dry and he stopped at a roadside stand to get a drink of ginger ale. From that time on, polyuria and polydipsia were severe. He stated that he drank 3 or 4 gallons daily. His weight rapidly fell so that he then weighed 188 pounds dressed. His height at that time was 5 feet, 7 inches with heels. The urine contained 7.2 per cent sugar, 2+ diacetic acid, the blood sugar was 0.33 (330 mg.) per cent. In the hospital he made an extraordinarily good record with small doses of insulin, became sugar-free and one month later he weighed 203 pounds, the urine was sugar-free, and the blood sugar was 0.11 (110 mg.) per cent; he was taking 5 units of insulin morning and night.

If such cases occurred with great frequency it would be easy to be convinced of the importance of nervous shock in relation to diabetes. Actually, however, the vast majority of patients become diabetic without any such shock. In this case, it is unreasonable to disregard the man's obesity, a common cause of diabetes, in order to accept a rare and hypothetical cause. Furthermore, in those cases of glycosuria accompanying real cerebral injury, true diabetes does not result, as illustrated by the following case:

Case 8517, a girl eleven years of age, had a sudden headache at 1 o'clock in the morning and became unconscious by 3 A. M. on December 1, 1929. In a nearby hospital the urine contained a large amount of sugar and during the next thirteen hours she was given 157 units of insulin in an effort to make the urine sugar-free. The sugar in the cerebrospinal fluid was 408 mg. per 100 cc., and a second lumbar puncture yielded fluid with 417 mg. glucose per 100 cc. The only blood sugar test gave 0.08 (80 mg.) per cent after 100 units of insulin had been given. I saw her on the second day when the presence of blood in the cerebrospinal fluid suggested the diagnosis of subarachnoid hemorrhage. She made an uneventful recovery, was sugar-free, required no further insulin after the first day; but in one year again had a spontaneous subarachnoid hemorrhage at which time she was observed at the Massachusetts General Hospital. On this occasion, no sugar appeared and she was not diabetic. In November, 1936, her family physician reports that she is well and at school.

**Effect of Trauma Upon Diabetes.**—The effects of trauma upon a known diabetic patient may be difficult to interpret and yet most serious in their consequences, as illustrated by the following case:

Case 4908, aged forty-seven years at the onset of diabetes in May, 1925, fell on the stairs on December 16, 1935, with an injury to her knee. The injury

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NEUROSIS

IN recent years, with the increasing incidence of heart disease and the widespread publicity about it, the problem of cardiac neurosis has assumed a place of great importance in medical practice. Almost daily we are confronted with cases that must be carefully studied and treated with this condition in mind, and, not infrequently, anxious or fearful members of a family may be as difficult to manage as the patient himself.

Cardiac neurosis (or psychoneurosis) in which there is actual fear or anxiety about the heart should not be confused with the equally common condition known as neurocirculatory asthenia although quite often the two occur together, and eventually the latter may cause concern about the heart in the patient, his family, or his physician. Any neurotic or psychoneurotic state may have cardiovascular symptoms associated with it or be in part or completely based on the belief of the presence of heart disease, even with no symptoms whatever. This is very different from neurocirculatory asthenia where symptoms such as palpitation, precordial pain, dyspnea of the sighing type, faintness, dizziness, tremor, sweating, and nervousness may be present to a marked degree without any particular apprehension about the heart. There may be, and often is, a coexisting anxiety neurosis of some sort in such patients but not necessarily a cardiac neurosis, though this may develop in the course of time.

Underlying every cardiac neurosis there is, as a rule, some



and being quite apprehensive he sought an opinion and advice regarding his heart.

On physical examination he appeared perfectly well and, except for a slight elevation of the pulse rate, perhaps the result of nervousness, no abnormality was found. The blood pressure was 145 mm. mercury systolic and 90 diastolic. The heart and lungs were quite normal on fluoroscopic examination, and the electrocardiogram was normal.

*Discussion.*—Here we have an illustration of a posttraumatic neurosis, with actual belief in the presence of heart disease (cardiac psychoneurosis), attributed by the patient to his chest injury. The family history of heart disease, the sudden death of another occupant of the car in which he was riding at the time of the accident, and his own chest injury all were factors in precipitating a full-blown neurosis in an already nervous, sensitive individual. There was no evidence of actual cardiac trauma in this case; the cardiovascular symptoms did not begin until four months after the accident and when they did appear they were typically those of neurocirculatory asthenia and not of a damaged heart.

Having carefully determined the absence of significant cardiovascular disease in such a patient, and having gained his confidence, the greatest single therapeutic weapon is reassurance. Ideas which have grown and taken abnormal proportions in the mind of a patient, largely due to fear and misinformation, must be dispelled firmly but without ridicule. The method of citing examples is a useful one in demonstrating that a particular case is not unique or hopeless, and if this is tempered by judicious sympathy and an optimistic attitude toward the future, much can be accomplished in giving hope, encouragement, and a new lease on life to persons who might otherwise be almost totally incapacitated by an ailment which has no organic basis.

*Case II. Neurocirculatory Asthenia Predominating.*—An Italian laborer, aged forty-eight years, had always been well and active except for two operations in 1923, one for right inguinal hernia, the other for "ulcers of the stomach."

On May 6, 1930, while working as a hod carrier, he fell from a scaffold 15 to 20 feet to the ground and landed on his back. The right tenth and eleventh

definite exciting factor. The occurrence of heart disease, especially sudden heart death, among relatives and friends, or even simply reported in the newspapers under dramatic headlines may initiate a cardiac neurosis in one who is ready for a neurosis of some sort. The finding by a physician of a heart murmur, trivial or not, of some disturbance of rhythm which may be insignificant, of hypertension great or slight, or of actual heart disease may be the exciting spark. Undue emphasis on some detail or actual misinterpretation of x-rays or electrocardiograms may provide the stimulus in the patient's mind. Subjective sensations may be the starting point, such as a disagreeable extrasystole, a paroxysm of tachycardia, or the numerous symptoms of neurocirculatory asthenia. Likewise various pains in the chest of cardiac (angina pectoris, coronary thrombosis) and noncardiac (cardiospasm, bursitis, muscle strain, pleurisy) origin may create fear of heart disease, and, therefore in the minds of most laymen, fear of sudden death.

It will be apparent in the cases that are to follow how important it is to recognize and treat these cases early, for a long established cardiac neurosis, particularly when complicating serious heart disease, may be almost incurable.

#### CASES ILLUSTRATING THE VARIOUS FACTORS PRIMARILY RESPONSIBLE FOR CARDIAC PSYCHONEUROSES, AND THEIR MANAGEMENT

##### I. TRAUMA

**Case I. Psychoneurosis Predominating.**—A Jewish tailor, aged thirty-nine years, was seen by us on September 13, 1935. He had always been well and active, but of a nervous disposition. His father died at sixty-three of cerebral hemorrhage; his mother has heart disease.

Ten months previously, on November 27, 1934, he was in a serious automobile accident, in which the driver was killed outright. The patient had several ribs and the right clavicle fractured, and was in bed for from two to three months. x-Rays taken shortly after the accident showed a "little arthritis of the spine and shoulders." When he began to move around again he suffered considerably from backache.

Four months after the accident he began to notice dyspnea on climbing several flights of stairs, had sighing and yawning respiration at night, and felt heartache at times for no known reason. He was convinced that these symptoms were evidence of serious injury to his heart as a result of the accident.

and being quite apprehensive he sought an opinion and advice regarding his heart.

On physical examination he appeared perfectly well and, except for a slight elevation of the pulse rate, perhaps the result of nervousness, no abnormality was found. The blood pressure was 145 mm. mercury systolic and 90 diastolic. The heart and lungs were quite normal on fluoroscopic examination, and the electrocardiogram was normal.

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Having carefully determined the absence of significant cardiovascular disease in such a patient, and having gained his confidence, the greatest single therapeutic weapon is reassurance. Ideas which have grown and taken abnormal proportions in the mind of a patient, largely due to fear and misinformation, must be dispelled firmly but without ridicule. The method of citing examples is a useful one in demonstrating that a particular case is not unique or hopeless, and if this is tempered by judicious sympathy and an optimistic attitude toward the future, much can be accomplished in giving hope, encouragement, and a new lease on life to persons who might otherwise be almost totally incapacitated by an ailment which has no organic basis.

**Case II. Neurocirculatory Asthenia Predominating.**—An Italian laborer, aged forty-eight years, had always been well and active except for two operations in 1923, one for right inguinal hernia, the other for "ulcers of the stomach."

On May 9, 1930, while working as a hod carrier, he fell from a scaffold 12 to 14 feet to the ground and landed on his back. The right tenth and eleventh

ribs were fractured, the spine was said to have been injured, and there were abrasions and contusions over the back. He was in a hospital for two weeks, during which time one of the contusions on his back, near the angle of the left scapula, became infected and required incision and drainage. Following his discharge from the hospital he was unable to return to work and for a period of five and one-half months he received \$18.00 a week compensation for his disability. At the end of that time his physician pronounced him fit to resume work, and the compensation was discontinued. Thereafter he began to have palpitation and dyspnea on effort, dizzy spells, and great weakness whenever he tried to do any work. He developed pain in the left scapular region, where the abscess was opened; this pain radiated anteriorly to the apex region of the heart, and became worse on any exertion. These symptoms have continued, to a greater or less extent, over a period of five years, during which time he has not worked. Repeated examinations by competent physicians have revealed no significant organic disease.

Physical examination in September, 1935, showed a somewhat thin, but well-developed man who appeared slightly ill and dejected. There was well-marked clubbing of the fingers, evidently of the congenital type, without cyanosis; this clubbing had always been present. The color was good. The throat was inflamed, apparently accounting for a cough which was present. The teeth were dirty and carious. The heart was normal in size, shape, rhythm, and sounds, no murmurs being present. The pulse was regular at a rate of 60; the artery walls were soft. The blood pressure measured 120 mm. mercury systolic and 80 diastolic. The lungs were clear and the abdomen normal except for the laparotomy and herniotomy scars. The reflexes were normal. The exercise test (going up and down a flight of stairs three times) was normal, the pulse rate rising to 112 and returning to 80 within one minute. Fluoroscopic examination, 7-foot chest plate, and electrocardiogram were normal.

*Discussion.*—This case, in contrast to Case I in which there is actual belief in the presence of heart disease, represents the frequent posttraumatic state, in which symptoms of *neurocirculatory asthenia* are outstanding; they may continue for years in some individuals, particularly in those who are naturally inclined to nervousness and vasomotor instability. Too much rest, without sufficient diversion and reassurance at the beginning, is likely to prolong the symptoms, as in this case, thus diminishing the possibility of successful therapy as time goes on. Disability benefits received over long periods of time, particularly when they exceed the usual wages, though doubtless due the patient in whole or in part, do not act to hasten recovery and often result in litigation for further compensation which in turn acts as an aggravating factor to the production of symptoms in persons with neurocirculatory as-



thenia. On the other hand, there are a few victims of accidents who become malingerers as a means of satisfying their "covetous wishes," but almost without exception they can readily be detected by obvious discrepancies between the history and the symptoms and signs. No malingerer should continue so for long in the hands of scrupulous physicians.

The management of neurocirculatory asthenia of long standing is difficult. It requires tact and perseverance in running down hidden factors which may be prolonging the symptoms. Where it is obvious that any physical impairment exists this should be corrected if, in the physician's opinion, no psychic harm will result. Even though a patient is greatly incapacitated by his symptoms he should be encouraged to engage in some gainful occupation, no matter how small, and in pleasant diversions, social or otherwise. Not infrequently patients with neurocirculatory asthenia are free of symptoms when under the stress of their daily work or in an amiable social gathering, their symptoms returning when alone or in an unpleasant social or domestic environment. Graduated exercises, improved hygiene, exemplary habits as to the use of tobacco and alcohol, and special attention to regularity in eating and resting should be emphasized as important factors in the management of neurocirculatory asthenia. Medicinal or sedative therapy is rarely necessary.

## II. NEUROCIRCULATORY ASTHENIA

Case III Neurocirculatory Asthenia Precipitated by Postoperative Hemorrhage and Nervous Shock Leading to a Cardiac Neurosis and a Severe Psychosis.—An unmarried Jewess, aged twenty-eight years, was seen by us on October 5, 1936. As a child she was tense and nervous, as was her mother, but she went through high school and two years of private school successfully. At the age of fourteen she had a tonsillectomy which she greatly feared. A postoperative hemorrhage after her return home necessitated a quick trip back to the hospital by ambulance. She was badly frightened by this episode and her heart beat rapidly and uncomfortably for a while. This subsided after the difficult time with her tonsils, but recurred five years later prior to an appendix operation.

At the age of twenty she had the shocking experience of having her fiancé die at the time of pneumonia. Following this the tachycardia and palpitation returned and persisted more or less. For several years she tried to lose herself

in exciting distractions but finally collapsed with "nervous prostration" and the certainty in her own mind that she had heart disease and did not have long to live. Subsequently she remained in bed for months and went through a typical schizophrenic episode with hallucinations and delusions mostly centering around death from heart disease.

In July, 1934, she was admitted to a private sanatorium, at that time in a convalescent state from schizophrenia. Improvement has been steady during the past two years but she still fears heart disease and continues to have such symptoms as dyspnea on stairs, sighing respiration, heartache frequently, occasionally momentary sharp stabs of pain over the heart, palpitation, giddiness, easy fatigue, tremor, and increased sweating, altogether typical of neurocirculatory asthenia. Although she admittedly would like to resume the responsibilities of her former environment she doubts her ability to do so on account of her heart, and returns to a frank interest in her heart function whenever such a possibility is mentioned.

She had been given digitalis early in her illness but its effect was unknown. Otherwise her treatment had consisted of rest, sedatives when necessary for sleep, and psychotherapy.

On physical examination she was alert and sighing occasionally. The heart was normal in size, sounds, and rhythm. There were no murmurs. There was no evidence of congestive failure. The pulse rate varied at the apex and wrist from 80 to 100. She was a little nervous at the time. The blood pressure measured 115 to 120 mm. mercury systolic and 70 diastolic. Fluoroscopic examination showed a small vertical heart. The electrocardiogram showed normal rhythm, rate 100, with a tendency to slight right axis deviation (normal for her build), and a normal chest lead.

*Discussion.*—A case of this kind offers a real problem in management. Not only are there a fear and a delusion of heart disease, but the many symptoms of neurocirculatory asthenia keep this fear alive, because they are interpreted by the patient as indicative of heart disease. It is necessary to offer a full explanation of neurocirculatory asthenia, so far as we understand it ourselves, at the same time reassuring the patient of its relative unimportance. Careful, sympathetic reeducation should be carried out as normal physical and social activities are resumed. Occasionally sedative or tonic medications may be used with good effect.

### III. ARRHYTHMIAS

**Case IV. Premature Beats.**—A traveling salesman, aged forty-five years, was first seen by us June 30, 1928, when he complained of discomfort in his chest consisting of heartache and brief stabs of precordial pain lasting a second at a time, occurring off and on through the day, but most noticed at

night when in bed. He had been working hard for many years without vacations and was nervously exhausted.

He had no other symptoms except that he occasionally observed at the moment of a stab of pain that the heart beat irregularly.

Physical examination at this time showed no abnormalities whatsoever except for occasional premature beats. The electrocardiogram was entirely normal, but the next month, in July, it showed auricular premature beats.

This patient was reassured, but felt quite certain that we were concealing from him the diagnosis of coronary disease with angina pectoris. He returned a half a dozen times within a few months, certain that he must have some serious heart disease. No evidence of heart disease was ever found. Gradually the intervals between visits increased until finally in September, 1932, four years later, he appeared still showing premature beats, but with a smile and a confession that he no longer thought we were concealing the truth from him, and that he probably did not have angina pectoris. Now in 1936, he is well, working actively, and undisturbed by his premature beats.

*Discussion.*—This man illustrates a condition, very commonly found, of distress and worry over the occurrence of extrasystoles, which may at times be so disagreeable in a sensitive person as to cause severe pain which may be confused with angina pectoris in careless history taking. It is obvious that very careful examination and reassurance at the start are the most important features. Reassurance may need to be continued in large frequent doses, as in the patient just discussed, but finally it proves effective. Later, heart disease may actually follow the finding of extrasystoles, but this seems, in the few instances in which one finds it, rather a coincidence. Although it is possible that in very rare cases heart disease, for example of the coronary type, may be ushered in with extrasystoles, we have no certain knowledge thereof. If the extrasystoles are very uncomfortable, one may use triple bromides,  $7\frac{1}{2}$  to 15 grains, three or four times a day for a few days or a week or two at a time, or quinidine sulphate 3 grains three or four times a day for a few weeks, or both these medicines together. The bromide acts chiefly to dull the perception of the extrasystoles while the quinidine tends to prevent them. Digitalis is generally contraindicated. It can itself produce extrasystoles. Finally, the advice that Mackenzie gave concerning the extrasystoles is also to be remembered, that after all factors such as excessive tobacco, fatigue, and

indigestion have been ruled out or controlled, exercise in the open air may be the best remedy of all.

**Case V. Paroxysmal Tachycardia.**—A twenty-eight-year-old accountant was seen by us in May, 1936. He had had pneumonia at the age of fifteen. Otherwise his general health had been good. At the age of thirteen years, while playing tennis, he had a sudden attack of rapid regular heart action, without pain or dyspnea, lasting a half hour. From that time until two years ago he was badly crippled by paroxysms of regular tachycardia lasting for hours at a time and recurring every few days on the slightest provocation such as the excitement of meeting a friend, carrying on business, or mild exercise. He suffered no pain but his attacks were attended by forceful rapid palpitation and such great apprehension of the consequences that he was, in fact, an invalid, unable to indulge in normal activity without fear of inducing a spell. He tried various medicines without benefit, but did not use quinidine or digitalis. No measures such as carotid sinus pressure or ocular pressure were used. In the year 1933 a tonsillectomy was advised and attempted, but the adrenalin, which was used in combination with the local anesthetic (novocain), initiated such a severe attack of palpitation that the procedure was abandoned. One year later his tonsils were successfully removed and he had slowly improved ever since. His attacks had become now less frequent and were of shorter duration. The last one had occurred one month prior to examination and was of two hours' duration.

On physical examination there were no abnormalities except for his slight build. He was obviously of a nervous and sensitive disposition. Fluoroscopic examination showed a normal-sized, vertical heart. The electrocardiogram showed sinoauricular tachycardia, rate 120, moderate right axis deviation consistent with his build, upright T waves in Lead I, normal P waves, and a normal chest lead.

In treatment this young man was taken out on the tennis courts and induced to play again, a thing he had feared and avoided for years. At first he was alarmed and bothered by the normal sinoauricular tachycardia that quickly ensued, but after brief rests and much reassurance he continued the game and finally was able to play without apprehension or symptoms.

**Discussion.**—This history is plainly that of a normal, irritable heart with paroxysms of tachycardia, undoubtedly paroxysmal auricular tachycardia, inducing great nervousness and apprehension which in turn, by their persistence, served to perpetuate a semi-invalidism. Just what part the tonsillectomy played in diminishing the frequency of attacks is problematical. At any rate the psychological effect was a good one. Of most importance, however, were reassurance and observation during the playing of tennis, at which time it was obvious that the

tachycardia that had troubled him most of the time had been sinoauricular and not paroxysmal, although originally true paroxysmal tachycardia had been to blame. With a regimen of increasing exercise this young man has rapidly improved.

#### IV. ORGANIC HEART DISEASE

The types of organic heart disease most commonly associated with a cardiac neurosis are the rheumatic, the hypertensive, and the coronary. Cardiovascular syphilis is in our experience rarely accompanied by a cardiac neurosis. Congenital heart disease and the cor pulmonale are in themselves rare and therefore present very infrequently a combination with cardiac neurosis.

**Case VI. Rheumatic Valvular Heart Disease (Mitral Stenosis and Aortic Regurgitation, Both Slight, and Neurocirculatory Asthenia).**—A single teacher, aged twenty-eight years, was seen by us on August 19, 1932. Her parents had died when she was quite young. She had always been sensitive and of a nervous disposition like other members of her family. Her tonsils were removed at the age of eight years. At the age of twelve years she was laid up for three months with an illness which she recalls as pneumonia, but which left a "leaking valve" in her heart. She had never been in robust health since that time. Following her original illness she had recurrence almost yearly for several years presumably of active rheumatic infection, but there had been no serious sickness for about ten years. Her immediate symptoms, which had been present for many years, consisted of insomnia, heart consciousness in the form of tachycardia and forceful palpitation, mostly at night, heartache, dyspnea of the sighing type, and nervousness. The slightest things worried her and she tired easily. Her symptoms were always worse in the early morning after a sleepless night. She was much concerned about the state of her heart.

On physical examination she appeared quite well but nervous. There were no abnormalities except for slight cardiac enlargement, a moderately loud apical systolic murmur, a slight middiastolic rumbling murmur at the apex, and a slight early blowing diastolic murmur along the left sternal border. The pulse rate was 72, the blood pressure measured 125 mm. mercury systolic and 70 diastolic. There was no evidence of congestive heart failure. Fluoroscopic examination showed a full-sized heart; the cardiothoracic ratio was just within normal limits. The electrocardiogram was normal.

When seen last by us, in April, 1936, she was still nervous and tired easily. Palpitation and heartache were prominent symptoms when she was very tired. On account of fear of overdoing she had given up regular teaching and was working irregularly as a substitute. But in spite of her fear and apprehension about the heart there had been no essential change in heart size or function over a period of four years.

*Discussion.*—This young woman is one of a large series of cases with a slight amount of rheumatic valvular disease in whom either the fear of the heart disease or the symptoms of neurocirculatory asthenia or both have created a cardiac neurosis. It is of vital importance in the proper handling of these cases to make it clear to the patient at the outset that there is not enough heart disease to produce symptoms or early disability or death. The neurocirculatory asthenia must be recognized, however, and treated intelligently by reasonable limitation of activity and strain as well as by reassurance.

**Case VII. Hypertension.**—A woman, aged sixty-nine years, was first examined by us in June, 1936. She had had severe diphtheria as a child, asthma provoked by a variety of factors off and on for thirty-five years, and severe grippe seven months previously. Hypertension of variable degree up to 250 mm. mercury systolic was known to have been present for four or five years. She was of a nervous, sensitive disposition and, in addition to her natural concern over her blood pressure, had been alarmed by physicians who had found such high blood pressure.

In 1932 she began to have some substernal oppression and palpitation on effort and excitement, and also at night, following attacks of asthma for the last two years, but she was not worried by this symptom. She had been slightly dyspneic all her life and this had been moderately increased during the past two years especially in the form of asthmatic breathing during an attack, on effort, or at night, at which time there was some orthopnea. All of her symptoms were worse following the severe grippe of the previous winter but were improving. She was very nervous, slept poorly, and was fatigued easily. In spite of this she insisted on taking 2 cups of strong coffee in the evening.

Her treatment had consisted of the use of belladonna, hyoscyamus, and bromide during the preceding year and of codeine and aspirin occasionally. Ephedrine and adrenalin had disagreed with her.

Physical examination showed very little out of the way. She was evidently nervous as had always been the case during her entire lifetime. The heart was slightly enlarged and there was a slight systolic murmur at the base. The pulse rate was a little high, measuring 96 at apex and wrist, largely the result of nervousness and the overuse of coffee. After a pleasant reminiscence of former days when patient and examiner had been neighbors on a lake shore during summer vacations, the blood pressure measured only 170 to 175 systolic and 95 diastolic. There was no evidence of congestive failure. The electrocardiogram was normal except for an increased heart rate.

*Discussion.*—Although this patient is well advanced in years and undoubtedly the victim of a moderate degree of

hypertension and coronary disease, she has been unduly alarmed as to the seriousness of her condition. With reassurance as to the future, advice to avoid nervous strain and excessive fatigue, a small amount of sedative medicine, the omission of coffee in the evening, and a quiet summer at the seashore, she reported great improvement at the end of two and one-half months. At that time the pulse was regular at a rate of 84, the blood pressure was 170 to 165 systolic and 90 diastolic, and her mental and physical improvement was obvious. She was further reassured, advised to continue along the same lines, and to have her blood pressure measured only every six months or less often.

**Case VIII. Coronary Thrombosis.**—A forty-nine-year-old physician was first seen by us in March, 1934. He had had lobar pneumonia at the age of twenty-one and had suffered from migrainous headaches for many years. His habits were exemplary except for the excessive use of tobacco. On account of easy fatigue and exhaustion he had consulted his local physician eighteen months previously but the only physical abnormality detected was a dead tooth which was later removed. A year afterward, on October 17, 1933, while sitting quietly, he noticed for the first time mild substernal discomfort lasting a few minutes. An hour later, while practicing golf shots, he was taken acutely ill with severe, tearing substernal pain radiating into the arms. The pain lasted for thirty-six hours in spite of  $\frac{1}{2}$  grain of morphine sulphate subcutaneously and several doses of pantopon. Fever was recorded up to  $101^{\circ}$  F. daily for a week, and the white blood count was much elevated, up to 25,000, during that time. A pericardial friction rub was heard on the third day of his illness and lasted for ten days. There were recurrences of the pain for a few weeks, but when seen in March there had been no pain for more than two months. His blood pressure had been low (90 systolic) for weeks, but was now normal. The electrocardiogram three days after the attack was typical of coronary thrombosis. He remained in bed for three and one-half months, hardly moving at all during the first five weeks of that period. The only medicines he received were narcotics and later theominal. He now felt fairly well and was sitting up two to three hours a day.

On physical examination he appeared slightly ill and his skin was sallow. Aside from slight cardiac enlargement no other significant abnormalities were present. The pulse rate was 68 and the blood pressure measured 125 mm. systolic and 80 diastolic. He was reassured and advised gradually to resume his practice and normal activity, which he did.

When seen by us again on August 6, 1935, he reported that he had been in excellent state of health and able to do light practice until the sudden death of a patient from coronary thrombosis in March, 1935. A few days after this he felt a mild chest pain—not severe—lasting a few hours. Fearing

another attack of coronary thrombosis he went to bed for six weeks but did not call a doctor. He had not returned to practice, and had led a quiet restful life. There was slight high substernal discomfort at times, but not on effort such as playing 9 holes of golf. He continued to smoke 20 cigarettes daily. On physical examination he now appeared well and the slight cardiac enlargement noted previously was the only abnormal finding. The electrocardiogram showed normal rhythm, rate 90, slight right axis deviation, low T waves in Lead I and upright T waves in Leads II and III.

With the reasonable assumption that his myocardial infarct had long been well healed and that most or all of his symptoms were the result of fear and anticipation of further trouble he was once more reassured and advised to omit tobacco and to return to work. When last heard from in November, 1935, he was in good condition and returning to the practice of medicine.

*Discussion.*—This case is an example of many others of cardiac neurosis following coronary thrombosis. It has been our experience that it is often more difficult to treat the nervous prostration in these cases than the coronary thrombosis itself, especially in physicians. The lesson is obvious, that a clear presentation of the whole situation should be made *early* in the illness to the patient, with ample reassurance, if justified, in order to prevent such a cardiac neurosis as developed in this case.

**Case IX. Coronary Disease Discovered by Electrocardiogram (Symptoms Due to Neurocirculatory Asthenia).**—A dentist, aged thirty-four years was seen by us in September, 1936. He had always been well and active, and a hard worker with no vacations. For four years he had been under much strain because of his mother's serious illness from hemiplegia, and had lost much sleep in caring for her at night. Six months previously, when very tired, he began to be troubled by aching pain, sometimes sharp, rather high in the left anterior chest, lasting a day or two at a time and not related to any effort or to meals. This had recurred frequently but had not been present during the preceding two weeks. Palpitation, slight dyspnea, dizziness, and faintness had occasionally been present with the chest pain, and he sighed frequently. He felt best while playing golf. Having access to medical literature he had read the books and was much worried by the ache in his chest, fearing heart disease. He had had no treatment except aminophyllin and sedatives without benefit. He was told that his electrocardiogram was abnormal.

Physical examination was entirely normal except for slightly enlarged tonsils. He was nervous and apprehensive of his cardiac condition. The heart was normal in size, sounds, rate, and rhythm. There were no murmurs. There was no evidence of congestive failure. The pulse rate at apex and wrist was 84. The blood pressure measured 115 mm. mercury systolic and 70 diastolic. The Wassermann reaction was negative. Fluoroscopic examination revealed no



abnormality. The electrocardiogram showed inverted T waves in Lead I, low voltage of the QRS waves in Leads II and III, and rather low voltage of the QRS waves in Lead I. In Lead IV the QRS waves were normal, but the T waves were upright.

This electrocardiogram is certainly indicative of a poor coronary blood supply in the region of the apex of the left ventricle, doubtless due to atherosclerosis and narrowing of the anterior branch of the left coronary artery, but it is difficult to say with any degree of certainty that serious clinical trouble is in the offing. Neurocirculatory asthenia and cardiac neurosis induced by fatigue and nervous strain were certainly responsible, in large part, for his symptoms, and although his future may be regarded as uncertain it may actually be fairly good.

*Discussion.*—This case illustrates forcibly the difficulty in treating a person whose symptoms are not those of heart disease but who nevertheless has important heart disease. It also shows the importance of the electrocardiogram in detecting coronary artery disease, the serious consequences of which may be forestalled or diminished through the avoidance of physical and mental strain and a quiet, sane manner of living.

#### V. MISINTERPRETATION OF SYMPTOMS AND SIGNS

**CASE X. Noncardiac Cause of Chest Pain (Muscle Strain).**—A physician, aged forty-eight years, was first examined by us on August 28, 1933. Except for a gangrenous appendix in 1918 he had always been well and active. For a number of years there had been a tendency to blanching and coldness of the fingers on slight chilling.

On August 19, 1933, feeling quite tired from his busy practice, he started on a vacation and became quite active physically playing golf and tennis and on one day he picked oysters. A few days later, on August 26, 1933, while dusting the roof of his car he suddenly felt a severe soreness in the anterior left axilla sufficient to cause him to stop what he was doing. For two days the soreness continued in dull form, but steadily decreasing, and movements of the left shoulder and deep inspiration made it worse. There had been some sighing respiration but no true dyspnea and no substernal or back pain. That same day (August 26) he had much gas and diarrhea and the latter continued slightly for two days. With the possibility of angina pectoris in mind he had taken nitroglycerin three times with no noticeable effect. He was much worried by the chest pain and feared heart disease.

Physical examination, fluoroscopy, and electrocardiogram revealed no significant abnormalities. He was reassured by this fact and advised to lead a normal but less strenuous life. His symptoms disappeared promptly and with the exception of influenza with intestinal symptoms the following winter he has been well.

*Discussion.*—In this case there is little doubt that the underlying factors in the production of his symptoms were fatigue, slight muscle strain in the pectoralis group of muscles, and perhaps distress from excessive amounts of gas in the bowel. Likewise, symptoms of such noncardiac conditions as bursitis, pleuritis, and cardiospasm may be interpreted by the patient as evidence of heart disease.

Of the greatest importance in the management of such cases, aside from the actual treatment of whatever noncardiac condition exists, is to be sure that there is no coexistent heart disease. This is not always easy, for even severe coronary disease may be present at times with only slight or suggestive clinical or electrocardiographic findings. When reasonably sure that symptoms are not the result of cardiac causes the patient should be urged to be normally active as soon as his condition warrants it.

**Case XI. Heart Murmurs, Especially the Functional Pulmonary Systolic Murmur.**—A little girl, aged four and one-half years, was examined by us in February, 1934. She was a small baby, weighing only 4 pounds at birth but otherwise normal. She was subject to frequent colds. Her tonsils had been removed in July, 1933, because they were enlarged. She had recently had chickenpox.

At the beginning of the school year in September, 1934, she was examined with the rest of the children and her mother was told that there was some abnormality of the heart. It was impossible to elicit any story of cardiac symptoms from the mother or the child herself. Nevertheless there was great concern on the part of the parents who felt that the child had a poor appetite and became tired too easily, and they were beginning to interpret every complaint the child offered as evidence of heart disease.

Physical examination revealed a very slight functional pulmonary systolic murmur, dispelled on full inspiration. There was no cardiac enlargement either by physical examination or fluoroscopy. The heart sounds were good, the rhythm was normal. The electrocardiogram was normal.

*Discussion.*—This case affords an excellent example of parental solicitude and alarm which, if allowed to continue without proper reassurance, may result in the development of cardiac neurosis, not only in the child as she grows older, but in the entire family. A slight pulmonary systolic murmur, such as was present in this case, is the commonest of all heart

murmurs and may be considered as being entirely within normal limits. The failure to recognize it as such may do immeasurable harm. Similarly, undue emphasis may be placed on murmurs due to organic changes, when in the absence of cardiac enlargement or disability, they may be, in fact, of little more importance than the harmless functional pulmonary murmur.

**Case XII. Unimportant Electrocardiographic Variations or Artefacts.**

—A young man, aged thirty-two years, was first seen by us on October 23, 1936. Except for hay fever he had always been well and active, but overweight. In recent years he had been overworking and smoking heavily. He had reduced his tobacco to 3 or 4 cigarettes daily. His father has angina pectoris.

In June, 1936, four months previously, he first began to be bothered by a little dyspnea in the form of air hunger with sighing respiration, occurring at any time, but mostly when very tired from overwork. One month later while in a barber's chair having a haircut he was seized by a sense of suffocation and after the haircut he had to rush outdoors for air. He then consulted a doctor who found him breathing deeply and rapidly. He was put to bed where he remained for four weeks with much sighing respiration at first and then gradual recovery. He was seen in consultation by a local specialist who made a diagnosis of "soldier's heart" after obtaining a normal electrocardiogram. But because of the persistence of some sighing he went to a distant clinic for study in September, 1936. An electrocardiogram taken there was said not to be wholly normal and he returned home with the impression that he was a probable "heart case." Since then he had been in a state of nervous apprehension, the sighing respiration had continued, and a new symptom consisting of a little headache had been present for about four weeks.

Except for apparent nervousness and obesity physical examination was quite normal. The heart was normal in size, shape, and sounds. There were no murmurs. The pulse was regular at a rate of 84. The blood pressure measured 140 mm. mercury systolic and 85 diastolic. A subsequent electrocardiogram was normal.

*Discussion.*—Here we have an example of a case of marked cardiac neurosis set off by a fear both by himself and by others that his sighing meant heart disease. Unfortunately, while he was convalescing from this state of mind and body his apprehension was stimulated again by overemphasis of some trivial variation of his electrocardiograms from the usual average normal. There was no evidence of real heart disease in his case.

Unimportant electrocardiographic variations that are most commonly misinterpreted as evidence of heart disease are slight grades of left and right axis deviation, inverted T waves in Lead III (and particularly total inversion of Lead III), very slight elevation or depression of the S-T segment in Leads II, III, or IV, slight slurring of the QRS complexes without widening, and P-R intervals of 0.19 to 0.20 second in duration. The commonest artefact, aside from those obviously due to motion of the patient, is a reversal of leads in applying the electrodes.

**Case XIII. Unimportant x-Ray Variations.**—A young engineer, aged thirty years, was first seen by us in November, 1922. He had had repeated attacks of rheumatism since the age of twelve, and valvular heart disease was known to have been present since the age of eighteen. Lately there had been a few orthopneic attacks and some dyspnea and palpitation on moderate exertion. Otherwise he was in good health. On physical examination he appeared well. There was a soft, blowing diastolic murmur along the left border of the sternum, and a slight middiastolic murmur at the apex, recumbent and after exertion. The pulse rate was 80. The blood pressure measured 140 mm. mercury systolic and 65 diastolic. There was no evidence of congestive failure. He was reassured and advised to lead a normal life.

Seven years later, in October, 1929, he was seen again. His complaints at that time were continuation of the dyspnea on exertion which had been present for many years, a little heartache now and then, especially when tired or on lying down at night, rapid pulse, and slight palpitation. He was much worried by his symptoms. He had been taking digitalis for a few days. Examination at that time was much as before except that he was overweight and the middiastolic murmur at the apex was less definite. The blood pressure measured 140 mm. systolic and 80 diastolic. Electrocardiogram showed sinoauricular tachycardia, rate 120, well-marked left axis deviation, inverted T waves in Lead I and flat T waves in Lead II. He was advised to omit digitalis and to lose weight, and was further reassured about his heart.

His third visit was six years later in January, 1936. He reported a fair state of health except for slight recurrences of rheumatism in 1933 and 1934, much nervousness and insomnia due in part to obligatory work at night in the past three years, and increasing dyspnea and fatigue during the past few weeks. He had again taken digitalis for a few days. He brought with him x-rays of his chest which had been interpreted as showing great cardiac enlargement. This had caused him and his family much concern. Again his findings were as before. There was a slight degree of cardiac enlargement, the slight aortic murmur was still present, but no mitral diastolic murmur could be heard. It was evident on fluoroscopic examination that the increased cardiac measurement on the films had resulted from adding the area of dulness outside the heart shadow, caused by epipericardial fat, to the transverse diameter of the heart. He was again reassured and advised to stop night work.

*Discussion.*—Many x-ray films of the shadow of the heart and great vessels are misinterpreted. Usually the error lies in including in the transverse diameter or cardiac area measurements the shadow of the epipericardial fat so often present, thus increasing the apparent size of the heart sometimes to a considerable extent, or in interpreting as aneurysm tortuosity of the aorta, mediastinal or lung tumor, or simple dilatation of the pulmonary artery. Such misinterpretation may result in a serious cardiac neurosis. It should be carefully excluded or quickly corrected if already made, with full reassurance of the patient.

#### SUMMARY

We have herewith presented 13 cases illustrative of the diagnosis and treatment of cardiac neurosis excited by the more common factors, namely, trauma, neurocirculatory asthenia, various arrhythmias of the heart, the knowledge of organic heart disease (rheumatic valvular disease, hypertensive heart disease, and coronary disease as examples), and the misinterpretation of symptoms, heart murmurs, electrocardiograms, and x-ray films.



## CLINIC OF DR. WILLIAM H. ROBEY

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### THE RECOGNITION AND TREATMENT OF PAROXYSMAL RAPID HEART ACTION

THERE are three conditions of heart action which attract the patient's attention more readily than any others, premature contractions, tachycardia and palpitation. Angina pectoris when not intense is often borne much longer because the frequently accompanying indigestion is regarded as a cause of either pain or oppression beneath the sternum. Most of the early symptoms of organic heart disease in the cardiac area are tolerated by the patient so long as rate and rhythm are not noticeably disturbed, but when they are, he hurries to the physician to learn their meaning and the physician must decide between a functional and an organic disorder. This decision is not always easy; sometimes it is very difficult.

*Simple or sino-auricular tachycardia* is a term used to indicate merely the increased rate caused by normal overactivity. The average cardiac rate in a man is 72 per minute, in a woman 76, and in a child 90. Some normal individuals who persistently have a slightly higher or lower rate without other changes, regard the rate as normal and we are unable to disagree with them. Most people recognize a normally increased rate and do not inquire about it; they know that if they hurry or are agitated the heart will increase in rate but it returns to normal as soon as the emergency is over. Often we test hearts by one of the many exercises which have been devised,

the stair-climbing test which is convenient, inexpensive and as efficient as any. The cardiac rate is taken while at rest and then the patient ascends 20 ordinary steps at a lively pace. Immediately the pulse is counted and is considered within normal bounds if the rate increases 20 beats and returns to its original count within five minutes. Many healthy hearts accelerate much less than 20 beats and will return to the original rate in a minute or two. Diseased hearts will often not exceed the normal heart in rate after this test but the return to the original count is slower. Naturally the physician selects the patients for this test with caution, and a considerable number exhibit sufficient signs of cardiac or circulatory disease or small endurance beforehand to make the test unwise or unnecessary. Sino-auricular tachycardia must be differentiated from auricular paroxysmal tachycardia because prognosis and treatment are quite different. If tachycardia has a gradual onset and offset it is probably due to loss of vagal control and is therefore due to some recognized cause outside the heart. We inquire carefully into the history of infectious diseases which may have been a cause of heart involvement and we examine the heart for evidences of disease, for undue or idiosyncratic reactions to tobacco, tea, coffee, and less frequently alcohol; into drugs like atropine which paralyzes the vagus, or adrenalin which stimulates the sympathetic nerves. I have just seen a young man of twenty-seven in whom no disease of the heart or any other organ could be discovered except a benign infection of the prostate which has existed for the last two months. His tachycardia has occurred, however, at long intervals during the last three years. Previous attacks may have been induced by overindulgence in tobacco and the more recent ones possibly by his infection. He has never had rheumatic fever. The urologist who sent him to me is trying to cure his prostatitis and I have cut down his tobacco. An electrocardiogram taken during an attack showed an auricular origin, normal sinus rhythm with a rate for auricles and ventricles of 100, a P-R interval of 0.20 second and a QRS of 0.06 second, with no axis deviation nor other abnormalities. A second electro-



cardiogram taken a week later did not differ from the first test except that it showed the rate for auricles and ventricles to be 75. About this time he was married and being anxious to have life insurance he attempted to take out a policy but frankly told the medical examiner about his occasional attacks of rapid heart action with the result that the insurance company has for the time being declined him. It is very important for us to prove that he has simple harmless tachycardia since no evidence of organic cardiac disease can be discovered.

Whether we are dealing with simple tachycardia or paroxysmal tachycardia the etiology is much more difficult in the young adult than in the middle-aged or elderly because in the young signs of heart disease are often absent.

Sino-auricular tachycardia is a regular rapid heart with gradual onset and offset generally due to the release of control of the sino-auricular node by vagus depression and sympathetic nerve stimulation.

The difference between simple and paroxysmal tachycardia is sometimes largely a matter of history. Lewis states that while the patient describes the abrupt onset, a statement of gradual ending must be received cautiously since in some patients long paroxysms end in a series of quite short ones or in a declining number of extrasystolic interruptions. Paroxysmal tachycardia usually is unexpected, whereas simple tachycardia often comes at definite times or is induced by some recognized act or some indiscretion. For example, I have a patient who is a healthy middle-aged man but for years the smoking of 2 or 3 additional cigars during an evening card game will bring on a simple tachycardia. The old rule is that the pulse rises about 10 beats in rate for every degree of fever. While most febrile diseases cause this rise, typhoid fever is an exception, the pulse being little elevated above the normal during the active phase of the fever but with convalescence it may rise as soon as the patient is allowed to sit up; putting the patient back to bed for two or three days will generally restore the heart to its normal rate. The increase is probably due not to the immediate effect of toxins but to the exhausting effect of

a long febrile disease on a heart which is then asked to do more than has been its habit during the course of the disease. Particularly diphtheria and poliomyelitis may paralyze the vagus nerve and abolish its control of the heart.

Infectious diseases rarely damage the structures of the heart, though occasionally pneumonia leaves an endocarditis. The great exception is rheumatic fever which need not be discussed at this time. If the victim of an acute infectious disease escapes the effect of its general toxemia, his heart likewise escapes. Even when the heart is made to beat rapidly during the course of an acute disease, the duration is short and if the heart was healthy at the onset of the infection, the comparatively brief acceleration is usually harmless. In 1918 some persons convalescent from attacks of so-called "influenza" died suddenly and it was said that their hearts had been damaged by the acute infection, but as a matter of fact these people in many instances were suffering from some previously unrecognized cardiac pathology before the inception of the acute disease.

*Hyperthyroidism* is a cause of simple tachycardia and palpitation. Few additional symptoms may be present but the basal metabolic rate is the key to the cause. This condition must be stopped because while not immediately harmful, a long continued thyrotoxicosis with its constantly rapid cardiac rate may lead to exhaustion of the heart muscle.

*Menopause* is also another cause and it is not unusual to have women during this phase present themselves because they are convinced that they have heart disease. Inquiry into their history and a careful physical examination will eliminate other possibilities after which the use of one of the ovarian extracts will frequently clear away this distressing symptom. A recent case is sufficient to illustrate this cause of simple tachycardia. An unmarried school teacher, fifty-two years old, complained of palpitation, pain in the heart area and at times a rapid action. There was no history suggesting cardiac inefficiency nor anything in the physical examination and laboratory tests which pointed toward heart disease. The symptoms

of pain and tachycardia were coincident with irregularity in menstruation and the use of corpus luteum extract, 5 grains three or four times daily, has entirely relieved her cardiac symptoms. Naturally this cause is arrived at by thorough elimination.

**Neurocirculatory asthenia**, so much studied during the World War but seen also in private practice, occurs in certain individuals who when subjected to new and agitating conditions develop a train of circulatory manifestations of which sino-auricular tachycardia is a striking sign.

A Jewish youth of twenty years with an excellent family history was seen because of rapid heart action, palpitation and cardiac pain which his family physician had diagnosed as "heart strain." As a small child he had scarlet fever and has had occasionally a sore throat without constitutional disturbances. He has never had any disease suggesting rheumatic fever. His appetite has not been so good during the last five weeks but his digestion and bowels have been normal. He takes a general diet, eats slowly, and does not use alcohol nor tobacco. Until the present illness he has considered himself in perfect health. Three years ago, after graduation from a high school, he secured a shipping position in a shoe factory and continued there very contentedly until the factory closed last summer. For a brief period he worked in a cleansing shop but the duties were almost too easy and after a short time he looked about for another job in the shoe business. He secured one but at the end of the fifth week he felt ill and saw his family physician who said that he had a weak heart. After three weeks in the wholesale shoe house he began to have rapid action (varying in rate, he explained), pain in the cardiac area, palpitation and occasionally nocturnal breathlessness. He described his work in some detail, working two or three times as the story progressed. He began work at 9 A. M., had one hour for lunch and then returned until 6 P. M. Three evenings a week he worked from 7 until 11. All this time he packed boxes with shoes and placed the boxes on shelves, or he sorted sample shoes, brought in by the traveling salesman, kneeling on the floor throughout the day. A boss shipper moved about among the groups of assistant shippers constantly urging them to work faster. He was a well-developed and well-nourished young man with normal teeth and throat and good color. There were no glands. The cardiac area by fluoroscope showed the great vessels to be 4.2 cm., the right border 4.5 cm. from mid-sternum and the left border 6.8 cm. There were no abnormalities in the shape of the heart. The impulse was not heaving. No murmurs could be detected in any position, even after exercise. The rate varied between 84 and 120 and usually began to rise with examination of the heart. Clearly the rhythm suggested sinus arrhythmia. The blood pressure was 110/70. The electrocardiogram showed a rate of 120 for auricles and ventricles. The P-R interval was 0.18 second and the QRS complex was distinct. The T wave was upright in all leads and there was no axis deviation.

deviation. The lungs, abdomen and urine were normal. The patella reflexes were hyperactive but there was no trembling nor did the electrocardiogram show somatic tremor.

The emotional state during the recital of the medical history, the tachycardia with varying rates, the cardiac pain, which is not uncommon in nervous persons with tachycardia and palpitation, and the exaggerated reflexes all suggested a sino-auricular tachycardia and an emotional state. It was quite similar to cases of mild neurocirculatory asthenia seen during the World War. I believe that when this young man secures a congenial occupation his cardiac symptoms will cease.

Let us consider now the second form of rapid heart action, *paroxysmal tachycardia*. It is apparently due to rapid and regular waves of excitation and contraction arising at some point in the auricular or ventricular muscle outside the normal pacemaker. In this respect it resembles premature contractions of auricular or ventricular origin. Auricular paroxysmal tachycardia is a very frequent disturbance of rhythm but not quite so common as premature contractions. Various factors such as fatigue, undue or sudden exertion, alcohol, tobacco, coffee, digitalis poisoning, infection and heart disease are causes. Extraneous factors may be removed and the results watched. As with premature contractions heart disease is often absent. That is our problem—is there heart disease? Diseased hearts are more often the subject of auricular paroxysmal tachycardia than normal hearts. Auricular paroxysmal tachycardia is rarely seen in infants and young children. It is common in adults of all ages, especially in young adults and in the middle-aged. In the young adult *mitral stenosis* is frequently accompanied by auricular paroxysmal tachycardia and, indeed, may be one of the lesion's earliest signs. A mitral systolic murmur which could be passed as functional in an otherwise negative heart takes on a different aspect if there are occasional attacks of auricular paroxysmal tachycardia. Such a case should be studied carefully during normal rhythm to hear, if present, the middiastolic murmur of mitral stenosis. A few years ago I saw a healthy-looking married

woman, forty years old, with her physician. He had known her for many years and had never discovered any heart lesion. She had had 4 children, conducted her household and engaged in several outside interests. After an evening party she was awakened in the night by the rapid action of her heart. My examination resulted in little but the finding of a regular rhythm with a rate of 180. She did not know how the tachycardia began but its ending was sudden. Later I had an opportunity to examine her and found in the mitral area a distinct diastolic murmur. Two months later her physician asked me to see her when the tachycardia was repeated and a month later he telephoned that she was having another attack but I found that the arrhythmia was auricular fibrillation. About two months later she did not come down to breakfast at the usual time and her husband going to her room thought that she was profoundly unconscious. Her physician found a complete left hemiplegia which was followed by death in a few hours. Thus we saw the complete picture of mitral stenosis with its auricular paroxysmal tachycardiac, auricular fibrillation and cerebral embolus in regular order of sequence.

I have just seen a physician, thirty-seven years old, who has been strong and well all his life but rather nervous when going through an ordeal. For several years when bird hunting he has had attacks of rapid heart action just at the time of shooting a bird. The tachycardia comes on suddenly and ceases with equal suddenness. Recently the end of an attack has been characterized by a brief arrhythmia which has alarmed him and it was this feature which prompted the examination. Anxiety over a patient or nervousness when giving testimony during a trial by jury does not induce tachycardia. The physical examination was entirely negative. The electrocardiogram showed normal sinus rhythm with a rate of 92 for auricles and ventricles; the P-R interval was 0.12 second and the QRS 0.06 second; the T waves were upright in Leads I and II; there was no axis deviation and only slight slurring of the R waves. Here is the history of an intelligent man who has auricular paroxysmal tachycardia with abrupt onset

and offset but absolutely no physical signs of cardiac pathology. Furthermore, he does not have tachycardia except at the time of making a shot. One cannot take this single symptom, occurring rarely in an otherwise healthy individual, as anything very serious. Yet why does he occasionally have it while another apparently healthy man under similar circumstances does not? That is difficult to answer but it is plain that such a patient, like one with an unsolved murmur, should be observed from time to time.

### SYMPTOMS

In most instances the individual is conscious of a rapid rhythm; occasionally he is quite unaware of it as is also the patient with premature contractions; this sometimes occurs in the insensitive or the very ill. Generally these patients complain of a rapid palpitation or of a disagreeable fluttering in the chest and sometimes a pounding in the head, neck and even the arms and legs. Sensitive persons may have dyspnea and heart pain. In damaged hearts dyspnea may be present, especially in attacks lasting several days. Congestion of the lungs and liver and even of the extremities may occur due to prolonged inefficiency of ventricular contractions and because the brain for the same reason may not receive sufficient blood, vertigo and even loss of consciousness may ensue. In premature contractions with very prolonged compensatory pauses, and high degrees of heart block, faintness and syncope may be observed for the same cause.

### PHYSICAL SIGNS

When we are consulted by a patient with increased cardiac rate occurring in periods of varying duration the medical history must be carefully considered. If it is an increased rate due to and immediately following an infection it is readily disposed of, or if we can determine that the tachycardia is caused by some exertion or indiscretion that is clear to the patient or his physician, that too can be solved. Simple tachycardia which begins slowly, lasts a short time, ends slowly and occurs infrequently is usually an unimportant phenomenon.

Its rate may vary in the same individual under different conditions. Auricular paroxysmal tachycardia may be recognized clinically by its abrupt onset and offset, its rapid, regular rate varying from 110 to 200, lasting a few minutes, occasionally an hour, sometimes several days. It usually, unlike simple tachycardia, has a marked uniformity of rate. The blood pressure is often normal or slightly decreased and as might be expected because of the lessened output of the rapidly contracting ventricle, the pulse is small. Sometimes during very rapid action, especially if prolonged, pulsus alternans occurs due to muscle fatigue or occasionally intraventricular block develops. These are merely temporary manifestations and are easy to understand when we consider how such a rapidly moving heart must fail to maintain an even output due to regularly varying compensatory pauses or how with such rapid contractions the bundle can conduct all the small impulses. They are purely physiological disturbances of rhythm due to rapid rate and not to sclerosis or other disease of the cardiac tissues. The electrocardiogram employed during a paroxysm points to the area originating the attack but the instrument should be used after subsidence, to study any possible variations from the normal which may be obscured by the rapid rate and which may help in the discovery of cardiac disease. Quite often no other physical signs are found.

#### PROGNOSIS

If we can prove that the patient merely has simple sino-auricular tachycardia by history and physical examination, we can dismiss the symptom as one of unimportance. Indeed, auricular paroxysmal tachycardia is often dismissed in the same manner but let us analyze this symptom. If it begins in early life and is repeated at varying intervals, sometimes months or years, it is, like premature contractions, often harmless and of little consequence provided no signs of cardiac disease can be discovered. We have known of patients who have had attacks of tachycardia or premature contractions occurring at irregular intervals, some thirty, forty or even fifty years,

where no disease of the heart could be discovered and where its efficiency remained normal. On the other hand, if auricular paroxysmal tachycardia occurs frequently or is unduly prolonged, it may produce exhaustion and lead to chronic invalidism. We all have seen cases, as Lewis pointed out many years ago, where paroxysmal tachycardia tends to recur with shorter intervals until there is an attack which persists and ends fatally despite all our efforts. *Ventricular tachycardia*, a rare and often fatal sign, sometimes comes at the end of a clinical picture of heart failure but this is a result and not a cause. We have already said that in young adults auricular paroxysmal tachycardia is sometimes an early symptom of mitral stenosis and where there has been a history of rheumatic fever or repeated attacks of tonsillitis, it may precede auricular fibrillation. If one looks at the muscle damage and distortion about a stenosed mitral valve it is not difficult to comprehend why ectopic disturbances of rhythm occur. When auricular paroxysmal tachycardia begins in middle life, even if few or any signs of cardiac pathology can be discovered, it has always seemed to me of more significance. The same may be said of premature contractions. Nocturnal dyspnea, substernal oppression or pain, and tachycardia have seemed to me to be equally important and are indicative of a degenerated heart muscle laboring against anoxemia during the lowered cardiac rate of sleep. Such a heart may show very little during a routine examination and I am so afraid of missing the nocturnal symptoms which the patient may not voluntarily mention that I have the questions carefully indicated on my history sheets.

#### TREATMENT

Brief attacks of infrequent occurrence usually do not require treatment, although certain very sensitive individuals whose attention becomes focused on their hearts may have to have something done. Even though our physical examination may be entirely negative and our statements very encouraging, still the consciousness of cardiac action and of disturbed rhythm make treatment necessary in many cases. Prolonged



and frequent attacks demand an attempt to abolish them. Treatment therefore consists in an effort to stop an attack and to prevent recurrence. A very brief attack is usually over before much can be done about it. The prolonged attacks generally respond more readily if the patient is put at complete rest, seated or recumbent, although this is not always so and then some type of exercise, such as raising the arms above the head or bending the body, may abruptly end the attack. Some people learn that a change of posture will effect a cessation of the attack and immediately practice it. After the patient has assumed a satisfactory position and the attack continues, it is well to try carotid pressure which consists of firm pressure with the tips of two or three fingers on the carotid artery just above the clavicle for several seconds up to a minute. The pressure should be firm enough to occlude the artery but not enough to cause pain. If we fail on the right side, the left may be tried. I have done this many times but with frequent failure. Again firm pressure on either eyeball with the lids closed may be tried. These are very old procedures but are worth while. Induction of vomiting with ipecac is sometimes successful. I know one Boston physician who uses this method in preference to all others. Lunigo many years ago advised emetine for the same purpose. Firm abdominal pressure or an ice-bag over the cardiac area is sometimes helpful.

Drugs are not very reliable. With persons who are nervous or distressed, bromides, 15 grains every three or four hours, may be used or rarely morphine,  $\frac{1}{6}$  to  $\frac{1}{4}$  grain, subcutaneously. One should be cautious, however, about the use of the latter drug in a condition which may frequently repeat itself. Digifolin may be injected subcutaneously or, better still, intravenously. 12 grains every three or four hours for 4 or 5 doses. Of course the patient should be under the observation of the physician during this time.

The *prevention of auricular paroxysmal tachycardia* is quite as unreliable as the treatment of individual attacks. All of those factors which we have already mentioned as causes

should be sought for and eliminated. Then there is the added assurance of the physician who makes a careful physical examination and is able to encourage the patient with a statement of his negative findings. Digitalis or quinidine sulphate may be used. These drugs should be tried separately, giving digitalis the first place in doses of  $1\frac{1}{2}$  grains two or three times a day for a week and then  $1\frac{1}{2}$  grains daily for several months. The dose may be varied according to its effect upon the cardiac rate. If digitalis does not produce the desired effect, quinidine sulphate may be tried beginning with 3 grains, when, after waiting for five or six hours and being well borne, the dose may be repeated and then continued at the rate of 3 grains every two or three hours until a maximum daily dose of 18 grains is reached. After three or four days the dose may be reduced to 3 grains three times a day and so continued for several weeks.

Stepp and Schliephake in 1925 reported full and almost instantaneous control of paroxysmal tachycardia by using 0.5 cc. of a 5 per cent solution of choline chloride intramuscularly. More recently this drug under the name of Mecholyl (Merck) has been strongly recommended for intramuscular injection during the attacks. It comes in 10 cc. ampules, which may be injected into the muscle. It has also been given in the intervals in wafers of 1.5 Gm. each, which the patient can use himself.\*

#### DIFFERENTIAL DIAGNOSIS

Differential diagnosis is fairly easy. Sino-auricular tachycardia, paroxysmal tachycardia, auricular fibrillation and auricular flutter must be separated. Sino-auricular tachycardia has a gradual onset and offset and a variable rate, the latter often being evident during an attack, while paroxysmal tachycardia has a steady rate with abrupt onset and offset. The duration of auricular paroxysmal tachycardia is generally limited to a few minutes, seldom longer than two weeks, especially in the earlier attacks. A tachycardia which persists for

\* This paragraph was taken from a statement by the author in the *Jour. Amer. Med. Assoc.* Oct. 3, 1936, No. 14, Vol. 107, p. 1153

months or years suggests auricular flutter. The electrocardiogram will show the greatly increased auricular rate and a 2-1 auriculoventricular block. Ventricular is rare compared to auricular paroxysmal tachycardia and the electrocardiogram is necessary to separate them definitely, although slight irregularities of rhythm suggest the former. Auricular fibrillation can scarcely be confused with any other type of rhythm; its marked disorder is outstanding.

#### SUMMARY

We have endeavored to define the characteristics of sino-auricular tachycardia and auricular paroxysmal tachycardia and to indicate the difference in treatment.

It is highly essential to combine with our treatment as optimistic an outlook as possible, particularly when no signs of cardiac disease can be discovered, since the patient's anxiety over even a simple tachycardia may plunge him into a state of cardiac neurosis.

Ventricular paroxysmal tachycardia is not so common, is generally the accompaniment of serious cardiac disease and can be differentiated from the auricular type by the electrocardiograph. Also, a slight arrhythmia is more apt to occur in the course of the ventricular type but auricular paroxysmal tachycardia, usually very regular, may terminate in slight irregularity.



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### SYNCOPE, COLLAPSE AND SHOCK: THEIR MEDICAL SIGNIFICANCE AND THEIR TREATMENT

#### SYNOPSIS

- I. Clinical features of congestive and noncongestive failure of the circulation.
- II. Syncope: clinical features; mechanisms; types.
- III. Treatment of syncope: specific measures; symptomatic remedies.
- IV. Collapse and shock: clinical features; mechanisms; types.
- V. Combined occurrence of congestive heart failure with collapse and shock.
- VI. Treatment of collapse and shock:

#### Specific measures.

1. Supply of deficiencies (water, salt, blood, oxygen, protein, glucose and heat).
2. Elimination of abnormal factors (sleeplessness, fear, pain, "toxins" and chemical substances).

Symptomatic measures (shock position, blood transfusion, glucose, sucrose, gum of acacia, strychnine, caffeine, coramine, cardiazol, ephedrine, benzedrine, epinephrine, synephrine).

VII. Summary.

VIII. Bibliography.

#### 1. CLINICAL FEATURES OF CONGESTIVE AND NONCONGESTIVE FAILURE OF THE CIRCULATION

Failure of the circulation is still considered by some as being synonymous with heart failure; hence efforts to treat this condition often consist in attempts to improve the function of the heart. In the daily practice of medicine, as a matter of fact, general circulatory failure of noncardiac origin

is as common as, if not more frequent than, circulatory failure of cardiac origin. When confronted with a patient with evidence of acute failure of the circulation, physicians should always attempt to answer the following questions: (1) Is the deranged state of the circulation primarily (a) of the congestive type ("backward" failure) or (b) of the noncongestive type ("ischemic," "hypokinetic," "forward" failure)? (2) Is it primarily of cardiac origin? (3) Is it primarily of peripheral vascular origin ("ischemic failure," "peripheral syncope and collapse" or "shock")? (4) Is it primarily a loss of blood volume ("collapse" and "shock")? (5) Finally, is it, as often is the case, a combination of these factors? If, through analysis of the symptoms, signs and technical measurements, these questions are answered correctly, the treatment of circulatory failure will be more successful; more lives will be saved or prolonged, and under any condition comfort will be brought to the patients.

Therapy will depend on which of these conditions exist. Indeed, *in different types of circulatory failure the therapeutic approach may be diametrically opposite*. Thus, a patient with air hunger due to a desperate attack of cardiac asthma will be relieved by venesection, whereas a patient with air hunger due to shock may die as a result of such a therapeutic procedure. Indeed, since the time of Hunter, Cooper and Broussais much harm has been done through indiscriminate use of bloodletting in circulatory failure. In instances in which a combination of types of circulatory failure are present, sound judgment and extreme caution are needed. Here, as in other therapeutic problems, "skill" and "art" are but the summation of rational clinical analysis (diagnosis) and synthesis (treatment).

Circulatory failure of the congestive type is always of cardiac origin and is usually spoken of as "cardiac failure." It is important to bear in mind, however, that heart failure may be of the noncongestive as well as of the congestive type. The chief characteristic of *congestive* failure is engorgement of the venous system, either in the pulmonary circuit or in the larger systemic circuit. The *clinical features are due to*

venous engorgement with resultant elevated capillary pressure and opening of reserve capillaries, and to tissue responses secondary to these circulatory changes.<sup>1</sup> Thus, dyspnea, orthopnea, Cheyne-Stokes' respiration, arterial anoxemia with cyanosis, pulmonary râles and edema, and, at times, hydrothorax are the usual manifestations of pulmonary engorgement; while distended superficial veins, cyanosis associated with increased oxygen utilization, dependent edema, hydrothorax, ascites, tender and enlarged liver and other manifestations of passive congestion of viscera are results of engorgement of the veins and of increased capillary pressure of the larger circuit. Clinically, in a given patient one usually finds evidence of a disproportionate congestion of the pulmonary circuit or of the larger systemic circuit. This is due to the fact that the lesions which result in congestion are usually localized in one side of the heart, and throw a strain predominantly on either the left or the right ventricle. This has led to the use of the terms "*left ventricular failure*," to describe cases in which the pulmonary circuit is engorged, and "*right ventricular failure*," to describe those in which the systemic circuit is engorged.

In congestive failure the arterial pressure may remain unchanged or may become lowered or elevated. The blood flow through the heart may be normal or decreased, and a normal or fairly normal peripheral circulation may be present, even in grave cases.<sup>1, 2, 3</sup> The velocity of flow through the individual pulmonary pathways is, however, reduced as a result of increased cross-sectional diameter of the capillary system due to venous engorgement.<sup>4, 5</sup> The circulating ("effective") blood volume is usually increased, and the total blood volume always increased,<sup>6</sup> in chronic congestive failure. This represents an important compensatory mechanism and a safeguard against collapse and shock.

Heart failure of the *noncongestive* or "anoxic," "ischemic" type is due to acute impairment of the heart as a whole, which results in a totally inadequate output of blood. Examples of this "forward" type of heart failure are found in the sudden

arrhythmias and asystoles, or in the more prolonged toxic, infectious or degenerative myocardial failures, such as occur in diphtheria or in senility. In such cases the manifestations usually present in congestive failure often do not occur, or are of mild degree and evenly distributed within both circuits. The total blood volume is unchanged, but the circulating volume is diminished. The large reservoirs of the greater circulation take up considerable amounts of blood, and manifestations of venous engorgement are absent or occur late.

The noncongestive type of circulatory failure is more frequently of *noncardiac* than of cardiac origin. It then results from a *disproportion between the total blood volume and the total vascular volume, and is accompanied by a reduction of the circulating ("effective") blood volume*. Either the total vascular volume increases, or the total blood volume decreases, or both changes occur simultaneously. The total vascular volume may be increased by the dilatation of vessels already open or by the opening up of vascular areas hitherto closed. The total blood volume may be decreased by hemorrhage, dehydration or diffusion of plasma as a result of various hemic or vascular changes. In any case, the result is a decreased return of blood to the right side of the heart and hence a diminished circulating ("effective") blood volume, a decreased cardiac output, lowered arterial and capillary pressures and, finally, anoxia of certain tissues.

It is the purpose of this discussion to emphasize the following considerations: (1) syncope, collapse and shock represent the same type of circulatory disturbance characterized by an *acute noncongestive* ("anoxic," "forward," "ischemic") failure of the circulation, associated with anoxia of certain tissues, particularly of the brain. (2) All three of these circulatory syndromes may be caused by many different mechanisms, but they are all similar or identical in nature. (3) The essential differences between the circulatory states in syncope, collapse and shock are quantitative rather than qualitative. All three syndromes are stages or degrees of the same fundamental type of circulatory failure, but with different



bodily effects and prognosis. (4) To search for a single cause of syncope, collapse or shock is to acknowledge lack of understanding of the problem as observed at the bedside. (5) For the correct therapeutic management, knowledge of the exact mechanisms of each of these syndromes is essential. The diagnosis of "syncope," "collapse" or "shock" is inadequate because treatment should always attempt to correct the specific cause, and only secondarily to improve the circulatory state through symptomatic measures.

## II. SYNCOPE

Syncope is a remarkable example of the noncongestive ("anoxic," "forward") type of failure of the circulation precipitated by nervous, cardiac or vascular factors. It is an acute and usually transient bodily state associated with sudden, partial or complete cessation of the circulation, with loss of power of locomotion and loss of consciousness. There are a number of associated manifestations involving practically every system of the body. The symptomatology and mechanisms of the various types of syncope have been described elsewhere.<sup>7</sup> The main characteristics of the circulatory state consist in a sudden fall of the arterial and capillary flow and pressure, and a decreased return of blood to the right ventricle. The veins usually are collapsed. As a rule the circulation within the central nervous system is particularly disturbed. One sees the manifestations of acute cerebral anoxia in its pure form. Attacks of syncope usually last only a few seconds or a few minutes. Because of their short duration, usually no after-effect is observed following recovery. As a result of the intensity of the changes, on the other hand, the manifestations are alarming, and in rare cases death may occur.

There are several types of factors which, singly or in various combinations, play a significant rôle in syncopal attacks: *cardiac* disturbances, such as vagal inhibition, angina pectoris, coronary thrombosis, dissecting aneurysm, heart block, and paroxysmal tachycardia; *vascular* derangements, such as postural hypotension, vascular crisis of hypertension;

*chemical* agents, such as sodium nitrite, nitroglycerin, anaphylactic, bacterial toxins; *reflex* mechanisms, such as vasovagal, vagovagal, carotid sinus, oculocardiac, pleural and pericardial reflexes; and *psychic* factors, as in vasovagal neurosis, Gowers' and Nothnagel's syndromes. Syncope is one of the most striking examples of the widespread and serious influence of psychic factors on the functions of various vital organs. In a somewhat arbitrary manner, depending on the underlying mechanism, we have differentiated some 16 types of syncope.

The studies reported previously<sup>8, 9</sup> indicate that unconsciousness associated with syncope usually is due to a sudden diminution of the cerebral circulation. A close correlation between the degree of ischemia and unconsciousness does not always exist, however, mainly because the simultaneous activity of reflexes frequently exerts a direct effect on the centers regulating consciousness. It is of interest that the same afferent nervous mechanism which is active in carotid sinus syncope is capable of producing attacks of unconsciousness of cardiac, vascular or direct central reflex origin, singly or in combination. Certain types of attacks of unconsciousness observed in syncope represent transitional states between unconsciousness of primary cerebral origin, usually associated with convulsions (fits), and unconsciousness of systemic circulatory origin (faints), often accompanied by milder seizures. We have emphasized elsewhere<sup>7</sup> the fact that the differential features of fits and faints frequently are more relative than absolute.

Syncope may occur in otherwise healthy persons and in persons who are gravely ill. In the majority of instances it is a benign, transient manifestation, but not infrequently, particularly in organic diseases, it may be fatal. Instances of fatal cardiac syncope are particularly common in patients with coronary disease. Such fatal attacks are apt to occur in the upright position during exertion. In cases of coronary sclerosis postmortem examination frequently fails to reveal the immediate cause of death. In this disease, as well as in coro-

nary thrombosis, there is present a considerably increased vagal reflex inhibition, as well as a tendency to ventricular ectopic beats and to ventricular fibrillation. Sudden death occurring within a few seconds in previously healthy subjects is usually due to ventricular fibrillation or, rarely, to sudden cardiac standstill. We have observed three instances of sudden cardiac syncope in apparently healthy and vigorous young persons who were recovering from an ordinary respiratory infection. Postmortem examination in one instance indicated that the cardiovascular system was normal. Fatal cardiac syncope may occur in elderly persons when they start to walk after prolonged bed rest. Postmortem examination again throws no light on the cause of death in such cases. Apparently we are dealing with a fatal vasovagal syncope in persons with unstable vasomotor mechanisms and with increased vagal tone.

The essential difference between syncope in the normal and in the diseased man lies in the ability to reestablish normal equilibrium. Whereas in normal subjects, owing to the presence of numerous emergency functions and to the reserve capacity of the organs involved, a return to the normal equilibrium is accomplished with relative ease and promptness, in diseased persons, on the other hand, because of damaged systems, a return to the normal level is more difficult, is usually slower, or may even not occur. Whenever death occurs unexpectedly and within a few seconds, the most probable cause is syncope and not acute organic lesions, such as cerebrovascular accident or coronary thrombosis.

The primary danger from syncope is its damaging effect on the central nervous system. With the decreased return of blood to the right side of the heart not only is the volume of blood flow decreased, but such blood as flows to the organs and particularly to the brain must be under unusually low pressure in the capillaries. The circulation in syncope is markedly influenced by gravity. Hence the circulatory disturbance is particularly severe in the orthostatic position, and the maintenance of this position is a serious threat to the patient's life.

## III. TREATMENT OF SYNCOPE

**Specific Measures.**—In the majority of instances of syncope, regulatory mechanisms of the body (autotherapy) take care of the condition. A close correlation exists between circulatory changes associated with syncope and the function of centers which promptly induce unconsciousness and relax voluntary muscles. Thus fainting, or falling to a prone position, associated with mild clonic convulsive movements, serves a twofold purpose: (1) the sensitive structures of the central nervous system are brought down from a "high ischemic level" to the level of the heart; and (2) the return of blood to the heart is made easier in the horizontal level, and is then further aided by the convulsions.

Selection of specific therapeutic measures depends on a knowledge of the underlying mechanism of syncope. In some instances of vasovagal syncope, psychic conflicts represent the trigger mechanism, and proper eradication of the emotional difficulties often results in abolition of the attacks. In cases of congenital or acquired loss of tone of abdominal vessels, proper mechanical supports may be effective. Ephedrine in doses of  $\frac{1}{4}$  to  $\frac{1}{2}$  grain (15 to 30 mg.) two or three times daily also may be useful. Reflex syncope, such as the carotid sinus, vagovagal, pleural and pericardial syncopes, may be abolished or prevented by surgical section of specific afferent nerves, or by application of local anesthetics over the nerve endings irritated during surgical manipulations. In the prevention of syncope associated with postural hypotension, abdominal supports, elastic stockings, ephedrine and ergotamine are useful. Some of the postural hypotensive syncopes are related to lues of the central nervous system or to anemia, and in such instances the specific treatment of these conditions will abolish the attacks. Syncope of central vasomotor origin such as occurs after the administration of local anesthetics, can be prevented or abolished by the barbituric acid derivatives and other drugs which decrease the lability of the vasomotor centers. In the abolition of syncope associated with bradycardia (Adams-Stokes attacks), epinephrine or ephedrine is

of great value. The prevention or abolition of syncope caused by tachycardia depends on specific treatment of paroxysmal auricular or ventricular tachycardia, or of auricular or ventricular fibrillation. Syncope associated with heart failure is to be treated by measures which improve the cardiac function. If syncope results from acute loss of blood, prompt restoration of the blood volume is the most efficacious measure.

**Symptomatic Treatment.**—If the exact mechanism of syncope is not known, or if specific measures cannot be instituted, the attacks should be managed symptomatically. This is particularly essential if a patient is in an acute attack. The immediate danger in syncope is cerebral and cardiac ischemia. One of the simplest measures for facilitating return of blood to the heart and hence to the brain is to place the body in a horizontal or "shock position" (Trendelenburg's position). Additional elevation of the legs and their massage, associated with cardiac and thoracic massage, may be of considerable help. If examination of the heart indicates that vagal inhibition is a factor, atropine, alone or with epinephrine, will be of aid. Similarly, in instances of bradycardia, epinephrine, ephedrine and benzedrine will raise the cardiac rate and functional capacity. If there is evidence of a marked fall in pressure without bradycardia or asystole, epinephrine is the drug of choice. If in acute emergencies epinephrine is given intravenously or intracardially, relatively small doses, such as 0.5 cc. of a 1:10,000 solution, should be given.

#### IV. COLLAPSE AND SHOCK

In patients who are suffering from serious diseases but whose circulation has hitherto been normal or at least adequate, one frequently observes a sudden, unexpected elevation of the cardiac rate associated with a fall in the arterial pressure and a change in the clinical behavior of the patient. The patient becomes anxious and restless, the face appears pale or ashen, and usually is covered with perspiration. The skin as a rule is cold, but it may at times be warm. The patient is unconscious and will respond, but the sphere of interest rapidly

narrows and cloudiness of sensation develops. Impairment of mental acuity encroaches on the patient without his being aware of it. After recovery, there may be amnesia of events occurring during collapse. If the collapse is severe the radial, dorsalis pedis and other peripheral arterial pulsations are thready or imperceptible, while the carotid and other centrally located arteries exhibit a high bounding but empty pulsation. Subsequently cyanosis of the cold fingertips and toes may advance toward the trunk. The veins are collapsed and the pressure in them is low. The blood flow through the heart and other organs is greatly diminished. The circulation becomes more susceptible to the influence of gravity, and the return of blood to the right side of the heart is greatly affected by changes in position. The respiration is quiet and shallow, or deep and somewhat slow, but there is no orthopnea. Frequently, as in syncope, there are manifestations of disturbance of certain vegetative centers. Sudden vagal inhibition manifested by cardiac slowing, gooseflesh, pyloric spasm, nausea, vomiting, acute dilatation of the stomach and perspiration may occur. Many of these symptoms are due to an irritative response to certain centers to acute anoxia (*syndrome of acute cerebral anoxia*). The significant rôle of the cerebral circulation in collapse and its relation to posture are shown by the behavior of patients who, when propped up in bed, promptly fall into stupor, but when placed in shock position at once regain consciousness. We have had opportunity to make repeated observations on the striking differences in the psychic and bodily responses of such patients in these two positions.

This condition of circulatory *collapse* usually lasts but a few minutes to a few hours. When recovery occurs the patient looks normal within a short time. In protracted and ultimately fatal diseases, as in sepsis, spontaneous recovery usually follows the first attack of collapse. Subsequently, however, not only are attacks apt to recur with increasing frequency, but each attack is of longer duration and responds less to medication. During one of these attacks death may occur rather unexpectedly.

It is also a common occurrence for a similar type of circulatory derangement to persist for many hours, or even for several days, with varying degrees of fluctuation. Such a circulatory state is usually called *shock*.\* The onset may be either insidious or sudden. The initial behavior of the circulation may be identical with that in collapse, or there may be a preliminary stage when the circulation is apparently overactive, with the color good, the skin warm, the pulse bounding, and the heart action snapping and vigorous. This is frequently seen in infections, deficiency disease, delirium tremens, cerebrovascular accidents, spinal anesthesia and traumatic conditions. Measurements indicate that the arterioles, at least in some organs, are dilated, but the low blood pressure readings suggest that the effective circulating volume even at this stage is reduced. Subsequently, however, certain significant changes occur. The patient becomes profoundly pale and his eyes gradually sink in their sockets, giving him an anxious expression. The nose and face appear pinched. The voice is feeble and hoarse. Movements of the body progressively decrease and there is general prostration. The body temperature may be elevated initially, but subsequently it gradually becomes subnormal. The patient loses interest in his surroundings, but if aroused he responds with exaggerated intensity, although vaguely. In this late stage, even if the blood pressure and circulating blood volume are reestablished, improvement in the patient's general condition usually lags behind, or often does not follow.

\* The use in the literature of the terms "collapse" and "shock" is confusing because of the various implications of these names. Many authors use the terms interchangeably. Some observers, however, describe as "collapse" a circulatory disturbance characterized principally by cold skin, cyanosis and a rapid feeble pulse, and as "shock" a syndrome with warm skin, good color, and bounding empty pulse. We agree that those two types of manifestations exist, but we believe that a differentiation between them is only of secondary importance as they represent but subdivisions or stages of the more fundamental disturbance which we call "collapse" and "shock." Regardless of what terms are used in this problem the emphasis should be placed, not upon the name of the disturbance, but upon the recognition and understanding of the underlying disturbance.

The main characteristic of the circulation in both collapse and shock is a decrease in the circulating ("effective") blood volume. In both states there is usually a diminished return of blood to the right side of the heart, associated with rapid heart rate, low arterial, venous and capillary pressures, and progressive stagnation of blood in certain vascular areas, usually in the "blood depots." Not all these features, however, are present in each case, or in each stage of the two syndromes. *The essential differences between collapse and shock consist in the time element of the circulatory disturbance and in the severity of the chemical and functional changes in the tissues.* In collapse the circulatory failure is usually of shorter duration, the changes are still primarily within the cardiovascular system, and the dysfunction may rapidly revert toward normal. In shock, on the other hand, owing to the long duration of circulatory failure, changes develop within the tissues, particularly in the central nervous system, and consequently a return toward a normal state is more difficult and slower.

In shock, as in collapse, blood may be pooled in various vascular areas. Depending on the nature or location of trauma, on the chemical agents, or on nervous factors involved, these "pooling" areas may be generalized or may be localized in only one extremity, in the skin, or in the abdominal viscera. The dilatation of the small veins and venules of many organs plays a particularly important rôle.<sup>10, 11, 12</sup> These vessels possess great active as well as passive capacity to alter their lumens. It is of interest that dilatation of these venous vessels often coexists with constriction of the arterioles.<sup>12</sup>

As a result of the persistent ischemic capillary circulation, producing anoxia of tissues and the accumulation of local metabolites, changes in the capillary permeability may occur in some or in all organs, with consequent loss of blood plasma into the tissues, which further aggravates the condition.<sup>11</sup> Unless there is acute hemorrhage, hemoconcentration follows. Judging from the clinical and postmortem findings, edema and dehydration of different organs may coexist, particularly if the development of shock is gradual. Apparently, on the one hand



plasma oozes from the blood into the tissues where there is damaged capillary permeability and, on the other hand, tissue fluids return to the blood from organs with normal capillary permeability. Thus, provided there is adequate fluid intake, one may see patients with peritonitis or with advanced diabetic collapse who have a dry tongue and sunken, soft eyes, and a dehydrated blood, coexisting with edema of the lungs and buttocks and free fluid in the serous cavities. The altered chemical nature of the alveolar and pleural fluids, as well as the reduced plasma proteins and elevated red cell counts in such cases, indicates that an appreciable amount of fluid enters into the tissues from the blood. The damaging effect of this process of transudation must be an important factor, though little definite information is available on this phase of the problem.

Great individual variation exists in the tendency to collapse and shock. Elderly persons, and patients with previously diseased cardiovascular systems develop collapse and shock under less strain and damage than do young, healthy persons. Furthermore, as judged from clinical observation, persons of the same sex and the same age group differ in their capacity to withstand damaging stimuli to the vascular system. Infectious diseases, chemical poisons, physical trauma and nervous stimuli of the same intensity produce fatal collapse or shock in one group but not in another. One is impressed at the bedside by the capacity of certain individuals to withstand severe, persistent "battering" of the vascular system by toxic, nervous and traumatic stimuli. The decisive factors in this variation in the susceptibility to collapse or to shock are the innate state of the nervous centers and reflexes, the "vascular tonus," and the "vitality" of the tissues in general.

The onset of shock is often gradual and insidious, with slow fluctuations, but with a steady downhill tendency toward the profound changes which precede death. Both collapse and shock may, however, appear with dramatic suddenness in the course of long-existing disease, especially in aged

persons, causing death within a few hours. Such collapse often develops without alteration in the intensity of causative factors. Apparently the nervous system and the cardiovascular system can stand but a given amount of total "bombardment" by abnormal impulses. When the limit is reached, rapid disintegration follows. Whether this is preceded by a progressive decrease in the "vasomotor reserve" is not definitely known. Evidence is available, however, that a progressive "exhaustion" of the vasomotor system is counterbalanced by numerous regulatory adjustments until the final "break" appears clinically.

As far as the circulatory changes are concerned, the difference between syncope, collapse and shock is mainly one of degree, as is demonstrated by the fact that the same *causes* and *mechanisms* produce syncope, collapse or shock, depending mainly on the duration of the attack. Thus, pleural shock from a spontaneous pneumothorax may cause only transient unconsciousness with hypotension and tachycardia of but a few seconds' duration (syncope), or it may cause the same type of circulatory changes of milder intensity but of longer duration, resulting in general prostration of several hours' duration (collapse or shock). When a patient with an infectious disease suffers from circulatory collapse even while in the horizontal position, syncope with unconsciousness and serious disintegration of the circulation may follow if an upright position is suddenly assumed. It is also of interest in this connection that when administered to normal subjects, sodium nitrite may induce syncope, collapse or shock, depending on the dosage administered and on the degree of tilting of the body. An analysis of the circulatory changes in such subjects reveals the same type of disturbances as occur in diseased persons. This again demonstrates that a single type of circulatory failure may have entirely different prognostic significance, depending on its *duration*, and particularly on the preexisting state of the cardiovascular and nervous systems.

The *causes* of collapse and shock are identical and they are numerous. Psychic and nervous factors, chemical agents

trauma, hemorrhage, dehydration, singly or in various combinations, are capable of inducing these states. The majority of chemical and nervous factors act on the peripheral circulatory system, producing dilatation, paresis and changes in the permeability of the minute vessels of various organs of the body. Other factors, however, act primarily on the "vasomotor" centers and hence indirectly influence the volume of the vascular bed. In the early stage of collapse and shock the disproportion developing between vascular volume and blood volume is compensated by regulatory adjustments, mainly through reflex mechanisms and the action of local metabolites. Subsequently, however, primarily as a result of anoxia of the central nervous system, these and other regulatory mechanisms begin to fail, and rapid disintegration of bodily functions follows.

In disease of the internal organs, such as occurs in the field of clinical medicine, neurogenic factors play a significant rôle, operating through afferent nervous impulses. It is known that afferent impulses, especially from the viscera, traveling through sympathetic and parasympathetic nerves, are particularly responsible for vasodilatation, shunting of blood and lowering of the circulating ("effective") blood volume. Afferent impulses from somatic nerves, on the other hand, are apt to cause a rise in blood pressure (Loven reflex). In previous studies, examples have been presented demonstrating that afferent impulses from a single branch or from branches of the sensory-vagus or sympathetic nerves may, in the presence of pathogenically hyperactive reflexes, produce instantaneous syncope or collapse (vasovagal, vagovagal, carotid sinus, oculocardiac, pleural, pericardial types).

It is essential to appreciate that *the level of the arterial pressure alone is not a decisive characteristic of the clinical severity of collapse or shock*. A patient with arteriolar vasodilatation of neurogenic origin may exhibit low arterial pressure but nevertheless may have a more effective capillary flow through the vital organs than a patient with normal arterial pressure accompanied by maximal arterial and ar-

teriolar constriction, also of neurogenic origin. In the latter instance the blood flow through the capillaries may be quite inadequate for tissue nourishment. In both instances, in spite of the opposite behavior of the arterioles, there may be considerable dilatation of the venous reservoirs. The collapse of fever is an example of the former type, while collapse due to sodium nitrite is an example of the latter type.\*

Collapse and shock may originate in a disturbance of the heart or of the peripheral vascular system; in either case failure of the central nervous system occurs secondarily, and this, in turn, further accentuates the circulatory failure. In other instances, collapse and shock originate in the central nervous system as a result of disturbance of the vasomotor centers, through pain, psychic factors, such as fear, local anesthetics, hypnotics and cerebrovascular accidents. Changes in the peripheral vessels and in the blood volume then develop, which so decrease the cerebral circulation that further depression and failure of the already disturbed nervous functions result. *Regardless of the original cause of collapse and shock, this type of failure of the circulation represents a tendency to a vicious circle in which the vascular reactivity and blood volume, on the one hand, and the central nervous system, on the other hand, are in close interrelationship.* In a given case of collapse or shock one or another of these factors may predominate.

In addition to the central nervous system, the functions of the kidneys and other organs will become impaired. As a result of low arterial pressure and concentrated small "effective" blood volume, renal function rapidly decreases and complete anuria often follows. This, in turn, leads to a disturbance of the acid-base equilibrium, which adds one more factor to the

\* It is often assumed that change in cardiac rate and fall in arterial pressure are reliable indications of impending collapse. This, however, is frequently not the case. In elderly patients, in particular, the change in the facial appearance (dropping of the facial lines), retardation and confusion of mental processes, stertorous breathing, cyanosis, pallor and perspiration clearly indicate to the experienced physician the onset of collapse at a time when the arterial pressure is still unaltered and the heart rate but moderately elevated.

vicious circle. In a similar way the disturbed function of other vital organs, notably the liver and the gastro-intestinal canal, may add to the increasing state of depression of the vital processes.

Collapse and shock are often designated after the causative agent or disease; for example, "traumatic," "hemorrhagic," "infusion" or "speed," "anaphylactic," "hemoclastic," "colloidal," "dehydration," "bichloride of mercury," "diabetic," "pneumonia," "barbiturate," "renal," "histamine." These terms, however, are of little value to the physician unless he understands the mechanism underlying each form. Often several types of collapse may occur under a single designation. In the collapse of pneumonia, for example, dehydration, fever or vasodilating substances (bacterial toxins), singly or in combination, may be the causative factors. Similarly, in diabetes, tissue acidosis, dehydration, loss of electrolytes and infection may be responsible for collapse. The treatment of the various types of collapse and shock will depend on which of these factors are responsible.

The designation of "primary" collapse and shock to indicate the acute circulatory failure of nervous origin, and "secondary" collapse and shock to indicate a similar state of the circulation in which chemical agents, bacterial toxins, anesthetics, trauma or hemorrhage are the causative factors, is not entirely justified. There is no evidence that there is an essential difference in the circulatory failure in "medical" and in "surgical" shock.<sup>14</sup> These terms at best serve but for the designation of types of shock occurring in medical and surgical conditions. In both types, hemorrhage, dehydration, and vasodilator, vasoparetic and central depressant factors are active and the various mechanisms leading to failure of the circulation must be determined. In the field of internal medicine collapse and shock play a more important rôle than in surgery. It is quite remarkable, therefore, that their various forms have not heretofore been studied in clinical medicine.

## V. COMBINED OCCURRENCE OF CONGESTIVE HEART FAILURE WITH COLLAPSE AND SHOCK

In the foregoing discussion it has been shown that nervous and vascular factors without heart disease are frequently responsible for disintegration of the circulation. We should like now to emphasize that the acute noncongestive ("anoxic," "forward") type of failure of the circulation often appears in combination with the congestive type of failure. Whenever a *previously healthy or compensated heart fails acutely, the clinical picture will be a combination of congestive failure and collapse or shock.* As was pointed out before, the features of collapse and shock often predominate. As a result of failure of the ventricles a large volume of blood is suddenly shunted into large venous reservoirs, and the arterial and capillary systems become acutely deprived of blood. Under such conditions the danger to the organism will be particularly enhanced if simultaneously active dilatation of the arterioles, capillaries and venules suddenly occurs, as a result of pain or some other factor. In studying the behavior of the hemodynamics of animals one frequently has opportunity to observe the "see-saw" effect of a cardiotoxic agent on the arterial and venous systems. Following the injection of such substances as heavy metals, hypnotics or arsphenamine, or following manipulation or acute anoxia of the heart, there is a rapid rise in the venous pressure in the left and right auricles and a sudden fall in the arterial pressure. As soon as the cardiac damage is rectified the elevated venous pressure falls and the arterial pressure returns to the normal level. In man, a similar type of circulatory disturbance is observed in acute cardiac accidents: after coronary thrombosis, during the administration of anesthetics, during surgical manipulation of the heart and during certain arrhythmias. Such patients exhibit orthopnea, pulmonary edema, air hunger, distended veins, rapid thready pulse, anxiety, and cold skin with beaded perspiration. If venesection is undertaken on such patients, we have observed that after the removal of not more than 200 or 300 cc. of blood frank signs of collapse may come to the surface. We should

like to point out also that when cardiac patients suffering from chronic congestive failure develop collapse and shock, the manifestations of congestive heart failure and venous engorgement often subside or even disappear, in spite of the fact that the impairment of cardiac function persists. We have had opportunity to note that in patients with chronic congestive heart failure due to rheumatic and syphilitic heart disease, during collapse and shock the orthopnea and dyspnea improve and the venous pressure approaches normal. This mechanism may even be life-saving in certain extreme attacks of cardiac asthma. In this condition there are manifestations of marked left ventricular failure associated with acute pulmonary engorgement. In the severe and prolonged attacks, manifestations of collapse are often added to the clinical picture of cardiac asthma, and the patient appears to be in extremis. Usually, however, it is at this very stage that spontaneous improvement sets in and the symptoms and signs of pulmonary engorgement subside. The distress of the attack has produced a secondary collapse, which in turn acts as a venesection. This is, then, one of the numerous instances of autotherapy of the body.

#### VI. TREATMENT OF COLLAPSE AND SHOCK

From what has been said of the mechanisms of collapse and shock, certain general conclusions as to the principles of treatment may be drawn: (1) treatment should be aimed at the elimination of the causative agents. (2) Treatment should as far as possible be preventive, or should be instituted early. In shock, in contrast to syncope and collapse, one deals with secondary changes within the tissues which cause a tendency to irreversible or difficultly reversible processes; one may therefore reestablish the circulating blood volume and the blood pressure with only slow or no recovery of the patient.

3. Symptomatic treatment of shock is of only temporary benefit, but it is of value in helping the patient during the period when the etiological factor is being eliminated.

**Specific Measures.**—The success of specific therapy will depend on the nature of the collapse and shock. Usually

attacks of collapse and shock due to the deficiency of essential intrinsic bodily factors are treated more successfully than those due to the presence of abnormal factors. In the "deficiency types of shock," water, electrolytes, blood, oxygen, protein, glucose and heat play particularly important rôles.

1. *Supply of Deficiencies.* (a) *Water and Salt.*—There is a remarkable tendency of the body to maintain the salt concentration at an even level both in the blood and in tissue spaces. When water is lost, elimination of salt follows, and vice versa. Hence the lack of these two substances is closely related and plays an important rôle in the causation of shock associated with many diseases. This has been emphasized recently by Atchley and Loeb.<sup>16</sup> The normal daily output of water in health is about 2 to 3 liters, and of sodium chloride, 15 Gm. In diseases associated with fever or with fistulous opening, but particularly in conditions associated with diarrhea or with vomiting, the water and salt loss may be considerably increased. It has been estimated that normally between 7500 and 10,000 cc. of fluid are secreted into the intestinal canal within twenty-four hours.<sup>16</sup> Whereas in health the greater part of this fluid is reabsorbed, in pathological conditions, particularly those associated with vomiting and diarrhea, most of it, together with its organic and inorganic constituents, may be lost. Unless corrected, such a fluid and salt loss rapidly leads to a reduction of the blood volume with hemoconcentration, and hence to collapse and shock. Collapse and shock of dehydration may also result from the indiscriminate use of gastric or duodenal drainage with suction, such as is in vogue at present in various surgical and medical conditions often already associated with a tendency to collapse and shock. We have observed instances of abdominal distention in which constant gastric suction produced the typical syndrome of dehydration shock. In the majority of instances of "diabetic collapse," of collapse and shock occurring in infectious diseases, in heat exhaustion, in adrenal insufficiency, and in biliary and pleural fistulas, water and salt deficiency are significant if not the sole precipitating factors. In these con-



ditions, therefore, a constant effort should be made to prevent such deficiency by the subcutaneous or intravenous administration of from 1000 to 2000 cc. of normal saline solution three or four times daily. In severe cases of collapse and shock the intravenous route is always the choice, as in these states fluid is poorly absorbed from subcutaneous depots as well as from the gastro-intestinal canal. It is important, however, that intravenous infusion should be performed slowly in order to avoid embarrassment to the heart. The normal heart can take care of the slow intravenous infusion of from 7000 to 10,000 cc. of fluid in twenty-four hours. If there is a possibility that the cardiac function is impaired, clinical estimation or actual measurements of the venous pressure should be performed. If the pressure rises above 10 cm. the infusion should be slowed or stopped temporarily. An average rate of 10 cc. a minute, or 1000 cc. in one and one-half hours, should be maintained. In case there is indication that loss of salt is the primary cause, 2 to 3 Gm. (30 to 45 grains) of salt can be given orally or parenterally in concentrated solution three times daily.

(b) *Blood*.—In patients with severe hemorrhage, blood transfusion promptly alleviates collapse. Blood transfusion may also be used as a symptomatic remedy to increase the circulating volume and elevate the arterial pressure. Infusion of whole blood rather than of a crystalloid solution is particularly indicated in the type of collapse and shock accompanied by increased permeability of the capillaries. In certain types of shock, however, even proteins and whole serum may leave the vessels and pass into the tissues.

(c) *Oxygen*.—Anoxia of tissues is of fundamental significance in collapse and shock. In certain types of collapse, such as the collapse associated with coronary thrombosis, emphysema, bronchial asthma, pulmonary embolus, pulmonary edema, and high altitude (mountain sickness or aviation collapse), lack of oxygen in the tissues plays a specific rôle. Such anoxia is due either to the fact that oxygen has difficulty in diffusing through the alveolar walls into the blood (anoxemia) or to the

fact that the oxygen is unable to diffuse from the blood into the tissues (anoxia) because of its low partial pressure. At an altitude of 4500 meters the saturation of the arterial blood is still 85 per cent, but the oxygen partial pressure drops from 100 to 50 mm.<sup>17</sup> In these types of collapse and shock the administration of oxygen results in rapid improvement.

(d) *Protein*.—Because in shock there is a tendency toward increased capillary permeability, loss of fluids into the tissues will be even greater if there is a low protein level of the blood. The latter, therefore, enhances the disintegration of the circulation. An effort should be made to maintain the proper level of blood proteins through good nutrition or through transfusion. That loss of serum may occur through open wounds or burns is well known. Less well known is the fact that repeated abdominal and pleural taps can deplete the protein and electrolytic content of the blood. We have observed cases in which the circulatory collapse and fatal shock occurring in association with cirrhosis were directly traceable to the repeated removal of fluid rich in protein and to the inability of the body to replace the loss. A simple calculation of the protein content of the fluids removed will indicate the severe draining effect of such procedures.

(e) *Glucose*.—In instances of "hypoglycemic shock" lack of glucose plays a specific rôle. Prevention of such a state consists in maintaining an adequate supply of glucose. Observation of patients with a high degree of hyperglycemia, whose sugar has been suddenly lowered to a normal level, suggests that this procedure may precipitate collapse.

(f) *Heat*.—Collapse and shock may be precipitated by loss of body heat, as in exposure to cold air or to cold water. Since the heat regulation is disturbed in all types of collapse and shock, it is important to prevent the loss of heat by applying warm blankets or by keeping the patient in a warm room. We have found that gastric irrigation with warm saline or warm bicarbonate solution is most effective in supplying the splanchnic area with heat. In instances of collapse associated with poisoning, such as in that due to morphine, the beneficial

response to gastric lavage instituted for the removal of the poison often depends on the stimulus to the splanchnic structures resulting from the heat supplied.

2. *Elimination of Abnormal Factors.* (a) *Sleeplessness and Fear.*—These factors play an important rôle in maintaining collapse. Induction of sleep with proper drugs is justified, but care must be taken not to use doses with depressant effect. This therapeutic problem has been discussed elsewhere.<sup>18</sup> Elimination of fear through reassurance is important in the treatment of both collapse and shock.

(b) *Pain* is a potent causative factor and it should be eliminated. Skill should be exercised in the selection of analgesics. Local counterirritants and analgesics may be helpful in reducing the dosage in the systemic administration of drugs which may have an undesirable depressant action on the vasomotor centers. Morphine should be used with judgment.

(c) *Toxins and Chemical Agents.*—Whenever collapse and shock are due to the action of chemical substances on the central nervous system or on the vascular wall, specific treatment is usually unsatisfactory. Many substances, such as bacterial toxins, immunological products, drugs and heavy metals, combine with structures of the vessel walls, and their elimination or detoxification cannot be accomplished effectively. Some of these substances, like histamine, epinephrine, acetylcholine and bacterial toxins, are rapidly "detoxified" when there is an efficient circulation: hence, if their source of entrance is eradicated, recovery rapidly follows. In this type of shock, therefore, therapy consists in treatment of the original disease (pneumonia, typhoid, burns, trauma, etc.) and in simultaneous maintenance of an efficient circulation, since even unstable substances are not "detoxified" if the circulation is in a state of collapse and shock. This we have had an opportunity to observe in patients who developed collapse and shock following surgical operation in which evipal was used as anesthetic. In shock due to heavy metals or other substances which form stable compounds with the components of the arterial, capillary and venous walls, the damage is often ir-

reversible and treatment of severe cases is frequently hopeless.

**Symptomatic Treatment.**—There are a number of measures which are useful in the treatment of collapse, regardless of its cause. In collapse and shock, as in syncope, the circulation is greatly influenced by gravity. The pooling of blood and, conversely, the return of blood to the heart, are greatly affected by changes in posture. We have demonstrated this in cases of collapse due to nitrite. Patients with collapse or shock should be kept in a horizontal position, or preferably in "*shock position*," with the head low and the body elevated. In acute collapse periodic elevation of the lower extremities is useful.

Dissipation of *heat* should be prevented by using warm blankets and by maintaining a high temperature in the sick room. If the patient has already suffered considerable heat loss and has a subnormal temperature when first observed, application of hot-water bottles alongside the body and the extremities is effective. Gastric and colonic irrigations with hot normal saline solution are also useful.

Further therapeutic measures should attempt: (1) to increase the circulating blood volume; (2) to reestablish the normal state of the central nervous system; and (3) to restore a balanced state of the vascular system.

Increase in the blood volume is usually most effectively accomplished by *blood transfusion*. As mentioned above, in cases of dehydration shock, infusion of saline or glucose solutions will be effective. In the majority of instances of shock, however, there is an increase in the permeability of the capillaries in one or more organs; hence crystalloid solutions rapidly leave the blood stream. For this reason, in such cases salt infusions can cause tissue edema in certain organs, while the blood and other organs remain in a state of dehydration. Intravenous infusion of *glucose* in the form of 100 cc of 50 per cent solution may temporarily elevate the osmotic pressure of the blood. Recently it has been claimed that sucrose leaves the blood stream more slowly than glucose; hence the osmotic

effects of sucrose are of considerably longer duration than those of glucose.<sup>19, 20</sup> Sucrose has been administered by slow intravenous injection in doses of from 50 to 200 cc. of a 50 per cent solution.

The use of 6 per cent *gum of acacia* in 20 per cent glucose and normal salt solution has been advocated. A volume of 300 cc. is infused at a rate of 5 cc. per minute. It remains to be established whether such a solution is without danger of late after-effects.

In instances of collapse where there is evidence of primary or secondary depression of the vasomotor center or reflexes, *strychnine*, *caffeine*, *coramine*, *cardiazol*, *ephedrine* and *benz-drine* are useful drugs. These substances increase the excitability of the vasomotor and other vegetative centers and reflexes. Strychnine, in addition to its effect on the vasomotor center and reflexes, increases the muscular tonus and activity. The latter effect aids the return of blood to the heart. The dose of strychnine varies with the condition of the patient. In collapse and shock associated with barbiturate poisoning we have administered subcutaneously or intravenously as high a dose as 10 mg. ( $\frac{1}{6}$  grain) at hourly intervals, and, as the patient's condition improved, have gradually reduced the dose to 2 mg. ( $\frac{1}{30}$  grain). We have found strychnine in doses of from 2 to 4 mg. ( $\frac{1}{30}$  to  $\frac{1}{15}$  grain), given at hourly or two-hour intervals, an effective remedy in acute collapse in infectious diseases and particularly in pneumonia. Caffeine sodium benzoate in doses of  $\frac{1}{2}$  to 1 Gm. (7 to 15 grains) intramuscularly or intravenously, coramine in doses of from 1 to 5 cc. of a 26 per cent solution injected slowly intravenously, and cardiazol in doses of from 1 to 5 cc. of a 10 per cent solution are particularly useful in acute collapse, such as develops during surgical operations, in infectious diseases and in cardiac disease. The improvement in the peripheral circulation observed following the administration of these drugs is secondary to an increase in the sensitivity and tonus of the vegetative centers. There is also a possibility that these drugs may exert a constricting effect on the venules

acting as blood depots, but there is not as yet adequate information to establish this point. Whether they can also influence capillary permeability through their central action is at present unknown.

Ephedrine ( $\alpha$ -hydroxy- $\beta$ -methylamino-propylbenzene) and benzedrine (benzyl-methylcarbinamine) are particularly useful in the prevention and treatment of collapse and shock associated with unconsciousness and coma, such as occur in poisoning due to hypnotics and anesthetics. Whether they exert a similar useful effect in other types of collapse has still to be established. These substances stimulate several centers, particularly those regulating consciousness. We have administered to patients with severe barbiturate poisoning 30 mg. ( $\frac{1}{2}$  grain) of ephedrine or 15 mg. ( $\frac{1}{4}$  grain) of benzedrine intravenously or intramuscularly at intervals of two hours. With clinical improvement the dosage should be reduced and the interval prolonged.

There is at present but scant pertinent information on the rational use of substances acting directly on the peripheral vessels. We know that in the majority of instances of collapse and shock there coexist arteriolar constriction and dilatation of the capillaries and venules. In another group, however, there is arteriolar as well as venous dilatation. It is also probable that these two types of vascular abnormality occur simultaneously in various organs in the same patient. The coexistence of such different vascular states offers an explanation for the difficulty encountered in attempting any routine treatment of shock.

A chemical substance which exerts a constricting effect solely on the venules will be of particular benefit in the treatment of collapse and shock, whereas a substance which simultaneously induces constriction of the arterioles as well may further impair the blood supply to the tissues. For this reason the indications for the use of epinephrine in collapse and shock are not entirely clear. In transient peripheral circulatory collapse, just as in syncope, especially where arterial and arteriolar dilatation predominate, the subcutaneous administration

of 0.5 to 1 mg. ( $\frac{1}{120}$  to  $\frac{1}{60}$  grain) will promptly elevate the arterial blood pressure and improve the venous return of blood to the heart. Similar doses will be effective also in collapse due to acute cardiac inhibition or to other types of bradycardia. In shock or in prolonged collapse, its use may be followed by temporary improvement but subsequently the circulatory failure frequently becomes accentuated, and a repeated dose may be harmful. There is evidence, on the other hand, indicating that the continuous infusion of an epinephrine solution of low concentration, which will constrict the venules but will not produce spasm of the arterioles, may be beneficial. *The effect of epinephrine on various types of vessels and on the heart depends, therefore, on the concentration of epinephrine in the blood.* For therapeutic purposes this concentration can best be controlled by intravenous infusions. In collapse a solution of 1:100,000 (1 cc. equals 0.01 mg.) infused at a rate of from 0.25 to 5 cc. per minute may be beneficial, and such a rate can be maintained for hours or even for days. Whether the effect of epinephrine may be different in certain types of advanced collapse because of the abnormal state of the arterioles, capillaries and venules, we do not know.

Synephrine (p-oxyphenyl-ethanol-methylamine hydrochloride), which has an effect similar in many respects to that of epinephrine, is also useful in acute collapse such as occurs after strenuous work, in the course of infectious diseases and during surgical manipulations. It has a more prolonged effect than epinephrine, but, on the other hand, it is a less effective vasoconstrictor. Our present knowledge does not justify its use in shock. In collapse a solution of 1:1000 at a rate of from 1 to 5 cc. (1 to 5 mg.) per minute may be given intravenously for one to two hours several times daily. It may be given orally and rectally in solutions of 100 mg. per liter.

The administration of pituitrin or of pitressin, the pressor fraction of pituitrin, in collapse and shock, is not justified in the light of present knowledge. In experimental animals and in man pitressin produces a lowered basal metabolism, markedly decreased cardiac output, decreased peripheral flow,

and lowered pulse rate.<sup>21</sup> Such circulatory effects do not furnish a rational basis for its use in collapse and shock. Nevertheless, it has been advocated in certain types of acute circulatory failure by those who have tried it clinically. Thus Wenckebach and Aalsmeer have found it benefit in the collapse and shock of "wet" beriberi.<sup>22</sup>

## VII. SUMMARY

Syncope, collapse and shock are syndromes of the acute noncongestive ("anoxic," "forward") type of failure of the circulation. The essential difference in the bodily changes occurring in each of these syndromes is quantitative rather than qualitative. For this reason a sharp clinical differentiation between them may in certain patients be difficult. The duration as well as the severity of the circulatory disturbances plays a decisive rôle in determining their prognostic significance. If the circulatory failure is prolonged, the secondary tissue changes due to anoxia become less easily reversible and finally irreversible. Syncope, collapse and shock frequently occur not only in their "pure" noncongestive form, but also in combination with the congestive type of circulatory failure. Rational treatment requires a knowledge of the specific mechanism underlying each of these syndromes, as well as an understanding of the nature of the secondary disturbances present. Both specific and symptomatic measures useful in the treatment of syncope, collapse and shock are presented.

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## CLINIC OF DR. ROBERT T. PHILLIPS

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### PRACTICAL MEASURES FOR THE MANAGEMENT OF CHRONIC ARTHRITIS IN THE HOME

Two million Americans, it may be conservatively estimated, are afflicted with acute and chronic arthritis. Not more than 15 per cent of this number, in all probability, are under medical supervision. The failure of the medical profession to find a specific therapy for chronic arthritis has led to a very general belief among laymen and even among physicians that very little can be done about it. Consequently, beneficial claims are made for a wide variety of drugs advertized in every newspaper and magazine. The suffering patient vainly turns from one treatment to another, follows the advice of family and friends, and finally is resigned to the prospect of partial or complete invalidism. The challenge to the medical profession which we constantly face from chronic arthritis and rheumatism has been accepted only in the last few years. More work has been done since 1926 to enlighten us on the problem than in all previous history. During the past ten years, it has become evident that while no specific therapy of proved value has been developed, many forms of treatment are available to us which, taken together, offer in the light of our present knowledge the best possible means of controlling this disorder.

There is no short cut in the treatment of rheumatism. For ten years now the American Committee for the Control of Rheumatism has been preaching the doctrine of a wide angle attack, with emphasis on efforts to restore, insofar as may be possible, the patient's general constitutional equipment to a functional level. This approach necessitates a careful

scrutiny of the individual's physiological activity in each of the separate systems, with a view to encouraging better function in those where deficiencies exist.

Few hospital staffs are adequately trained to care for the arthritic. Until the profession itself is awake to its responsibility, an aroused public opinion cannot be expected to face this scourge as it has faced the problems of tuberculosis and cancer. Sanatoria for arthritis may come in the future, but for the present, the pertinent question is what to do for the arthritic who must remain in his home.

After a careful appraisal has been made of the patient's constitutional state, and the various functional deficiencies noted, a program should be established for him to follow out at home. In order to visualize the possibilities in establishing such a daily routine for a patient, I have tabulated the elements of treatment in the accompanying tabulation. The remainder of this paper will be a consideration in some detail of practical methods of therapy under the following headings:

- |                              |                          |
|------------------------------|--------------------------|
| 1. Rest and exercise.        | 5. Vaccines.             |
| 2. Special physical therapy. | 6. Occupational therapy. |
| 3. Orthopedic aids.          | 7. Drugs.                |
| 4. Diet.                     | 8. Psychotherapy         |

**1. Rest and Exercise.**—Rest is the first and most important method of treatment in arthritis; rest for the affected joints locally, and rest very often for the body as a whole. When confined to bed, the patient should not be allowed to occupy for indefinite periods the position most comfortable for him to assume. He should be instructed to practice postural exercises three times daily after meals. The bed should have a firm, nonsagging mattress. The pillow being removed the patient first lies in the hyperextension or horizontal position, the hands placed behind the head or neck to help raise the ribs and flatten the dorsal spine. A small pillow may be placed under the chest, and in the beginning several small pillows may be used to support the knees, these pillows being removed as the hyperextension positions can be taken without too much discomfort.

## OUTLINE OF THERAPY FOR THE MANAGEMENT OF CHRONIC ARTHRITIS IN THE HOME

## 1. Rest and Exercise:

Bed exercises.  
Breathing exercises.  
Sitting exercises.  
Standing exercises.  
Posture training.  
Muscle training.  
Overhead frame.

## 2. Physical Therapy:

Fomentations.  
Paraffin.  
Baths.  
Massage.  
Baker.  
Foot soaks.  
Hot-water bottle.  
Electric pad.

## 3. Orthopedic Aids:

Flannel bandages.  
Elastic bandages.  
Adhesive strapping.  
Thomas collar.  
Plaster splints.  
Corset, brace.  
Foot plates.  
Arch cuffs.  
Calipers, crutches.

## 4. Diet

Fresh fruits  
Fresh vegetables  
Cod liver oil  
Low carbohydrates  
Feeding between meals  
Salts and orange juice  
Hot abdominal packs  
Isulin  
M.M.  
Weight reduction

## 5. Vaccines:

Subcutaneous.  
Intramuscular.  
Intravenous.  
Autogenous.  
Typhoid.  
Foreign protein.  
Dosage.  
Frequency.

## 6. Occupational Therapy:

Knitting.  
Painting.  
Weaving.  
Woodworking.  
Modeling.  
Rug making.  
Carpentry.  
Games.  
Hobbies.

## 7. Drugs:

Salicylates.  
Arsenic.  
Potassium iodide.  
Iron.  
Sulfur.  
Cinchophen.  
Thyroid.  
Follicular hormones.  
Opiates.

## 8. Psychotherapy:

Optimism.  
Encouragement.  
Confidence.  
Supervision.  
Patience.  
Sterile hypos.  
Placebos.

After thirty minutes, the "face prone position" is assumed for a similar period. In this instance the patient is instructed

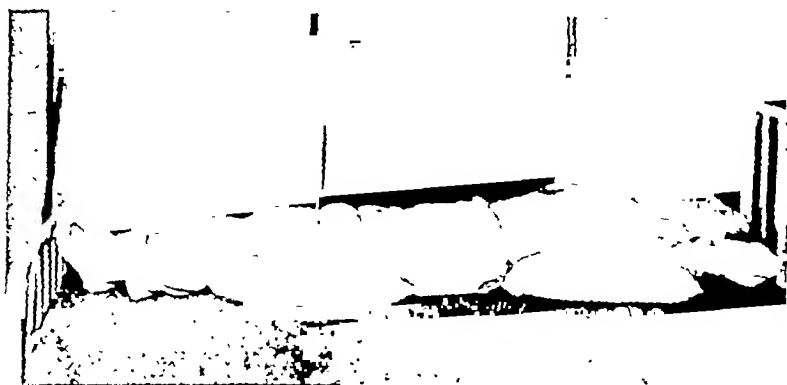


Fig. 31.—Hyperextension position with the body in a horizontal position with pillow under the knees and chest. The arms are extended over the head to help raise the ribs and flatten the dorsal spine. Note how the thorax is raised to the position of full inspiration encouraging free excursion of the diaphragm.

to lie on a pillow placed lengthwise under the chest and abdomen. The purpose of these positions, which are described

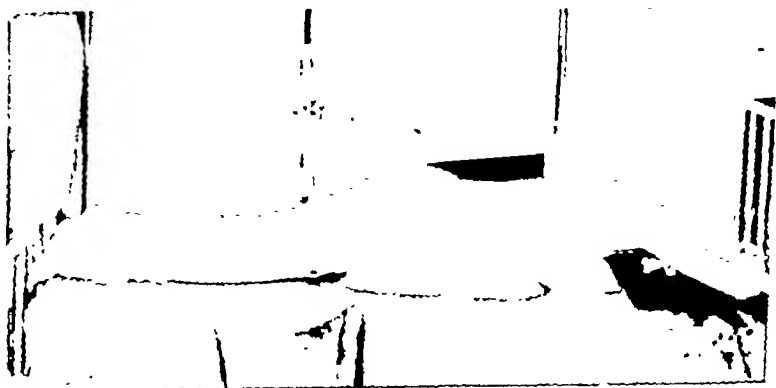


Fig. 32.—"Face prone" position. The patient is lying prone with pillows under the abdomen and pelvis. Note the flatness of the back and the fullness of the chest.

in the book "Body Mechanics,"<sup>1</sup> together with other exercises for posture training, is to counteract gravitational effects which

increase the sag of the organs and the strain on the body as a whole. These two positions represent the nearest approach we have to complete physiological relaxation. The elevation of the diaphragm encourages the development of better circulation and muscle tone in that organ while at the same time a more active circulation is permitted through the vascular channels of the abdominal cavity and the structures contained within it. Respiratory movements increase in range, developing a greater vital capacity.

Muscle training exercises are easily done whether or not the patient is confined to bed. For an outline of measures useful in developing muscle control and improved posture, the reader is referred to the above-mentioned book. My primary purpose in touching on this subject is to suggest the opportunities for educating the patient through daily practice to get his body into better condition to cope with his arthritis. For bed patients a simple overhead frame may be erected. A bar for the hands and elastic loops for the legs will provide the means for additional exercise not possible otherwise. Rest for the joints locally will be considered under orthopedic aids. It should be borne in mind that constitutional rest is invariably beneficial to the local manifestations.

**2. Special Physical Therapy.**—Heat in its various forms remains the chief agent of physical therapy for the arthritic patient. I do not believe that the more elaborate forms of electrotherapy have much, if anything, to offer that is superior to the old-fashioned hot fomentations or the dry heat from an inexpensive electric light baker. Details for making a home-made baker may be found in a small pamphlet entitled, "Useful Therapeutic Measures," published by the Council on Physical Therapy of the American Medical Association. Fomentations are best given by wringing out a woolen cloth which has been soaked in hot water, after which the cloth is wrapped about the part to be treated and covered with a heavier dry towel which serves to prevent the heat from escaping too rapidly. This procedure may be safely carried out once a day in most patients and twice daily if the patient has no temperature,

circulatory insufficiency, or other constitutional disturbance.

Massage may follow the application of heat with benefit. It should be remembered, however, that the application of massage should never add by trauma to the inflammation which may be present already in an affected joint. Hence, massage should be practiced in the neighborhood of, but not immediately over, the involved joint. The strokes should be in the direction of the venous flow. Fifteen or 20 strokes to the minute for a period of one-quarter hour will suffice for the usual treatment. The involved limb should be moved by the patient himself through as great a range of motion as is possible without pain twice daily. Passive motion within the painless range at the time massage is done will encourage the patient in this regard. Active motion, that performed by the patient unassisted, is to be encouraged. He must be taught to do what he can for himself, within the limits of his physical resources.

Melted paraffin is an excellent way to apply heat to arthritic joints, and this method may readily be carried out in the home. No equipment is required other than a 5-quart container or double boiler, 8 pounds of wax, obtainable at any filling station, and a burner. The wax melts at a temperature of 120° F., and the patient will be able to dip his hands safely in the wax when it starts to solidify over the top. Five or 6 coats will give the patient a pair of warm gloves which are then wrapped in a towel until the heat is dissipated. The wax may be painted in layers over larger joints. One treatment daily will be sufficient.

Warm baths at home should be employed for their mildly stimulating effects upon the circulation, as well as for their sedative properties. Under-water massage for those who may take tub baths should not be overlooked by reason of its marked sedative influence. Foot soaks are available in any household, and where swelling or edema is present, magnesium sulphate may be added to the water, 1 ounce to the gallon. The hot water bottle and the electric heating pad are also readily available sources of heat, and will do, in my opinion,



quite as well as more expensive and time-consuming measures as, for example, iontophoresis.

**3. Orthopedic Aids.**—The more fundamental orthopedic aids to the treatment of arthritis can be carried out almost as well in the patient's home as in a hospital. Our point of view in this regard is directed toward the protection of joints and the prevention of deformity. Flannel and elastic bandages are readily available and should be used more often than they are. An acutely inflamed joint should be well wrapped to give support to the joint structures, thus favoring subsidence of the inflammation. For elbow or knee, the preliminary application of liberal amounts of sheet wadding followed by flannel and elastic bandages usually effects a prompt reduction in acute processes. Adhesive strapping may be applied in criss-cross fashion to fingers, wrists, elbows, shoulders, knees, and ankles with good effect when swelling is present.

It is an error to presume that an arthritic joint will tend to stiffen unless motion is kept up at all costs. The fallacy of this notion, which was formerly widely preached by the medical profession, has been clearly demonstrated by Goldthwait, Swaim, and their associates at the Robert B. Brigham Hospital. For a dozen years patients at this institution have been provided with light plaster splints molded to the individual joint where inflammation was present. In no instance has this form of therapy led to ankylosis. While the application of plaster in the home may be attended with certain difficulties, it is entirely possible to provide home patients with short plaster arm supports in those cases where the wrists and fingers are involved. Such a "shell" can be quickly made in the following manner. Cut a piece of  $\frac{1}{4}$ -inch felt, 5 inches in width, extending from just below the bend of the elbow to just beyond the fingertips. Along one side, cut an indentation for the thumb. Two rolls of plaster are turned back and forth over the felt. The wet splint is then applied to the forearm and hand, felt side to the skin, a gauze bandage holding it in place. While it is hardening, the hand, wrist, and fingers are held in the position desired, usually with the wrist in extension



Fig. 33.—Three types of plaster hand "shells," each made with one roll of plaster. They can be made in a very few minutes at the bedside and molded to support the joints in the desired position.



Fig. 34.—Types of leg "shells." *Above:* Short foot boot, useful for protecting the ankle and maintaining good position of the foot. *Center:* Long leg "shell" employed for relaxing the knee joint and correcting flexion deformity. Note the extension on the toe to carry the weight of the bed clothes. *Below:* Posterior walking slab.

and the fingers in midflexion. After drying, the splint is trimmed with adhesive tape. Such an appliance will effectively immobilize tender, actively inflamed joints, preventing subluxation of the carpal joints and ulnar deviation of the fingers. The splint should be worn day and night for the first week, being removed for fomentations, wax, massage and exercise. In like manner plaster "shells" may be fitted to the lower extremities. Outward rotation of the tibia and foot can usually be prevented in this manner. The plaster splints can be very effective in supporting the joints in their best positions favoring normal function. By changing the "shells" once a week, early contractures can usually be corrected.

When a patient is getting up after prolonged bed treatment, posterior walking slabs may be made in the same manner. These will be fitted from the mid thigh to just below the calf, and will be bound on with flannel bandages. In this manner the joints will be supported in weight bearing, while at the same time the additional strain of motion will be avoided.

Medical men should get over their unwillingness to handle plaster, particularly with respect to its use in arthritis. Some of the medical supply houses are now putting up plaster bandages in neat, convenient packages, which renders the material available to all, in a form ready for instant use. The use of plaster as here advocated does not imply that it is time-consuming or that special training is necessarily required. A conscientious physician will find the few extra minutes it takes well worth while in results achieved. The more extensive use of plaster as, for example, the complete extremity cast, body jacket, or spica, are of course scarcely possible to manage in the home.

The patient with neck symptoms will be grateful for a Thomas collar, which can be made at his home in a few minutes. A piece of cardboard is cut approximately 4 inches in width, curved high to fit just under the ears and cut out below to fit over the trapezius muscles. It is also cut to dip down in front to accommodate the distance between the clavicles and the mandible. The collar fastens in back of the neck



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with a buckle or gauze tie, and thus the weight of the head is taken in part directly upon the shoulders, relieving the strain on the cervical spine.

Such accessory apparatus as a well-fitted back lace corset for women, an abdominal belt for men, steel back brace, foot plates, calipers, and crutches, may be provided in the home, but for such equipment it will be best to confer with an orthopedic consultant. The majority of deformities attributable to arthritis are preventable, but good results will not follow sketchy therapy. These orthopedic aids are of prime importance, and should be used to full advantage as early in the course of the disease as possible.

**4. Diet.**—There is no one type of diet applicable to all patients with chronic arthritis. In general a dietary high in vitamin-containing foods, moderate in caloric value, with liberal quantities of fresh fruits and vegetables is most suitable. In my opinion a restriction in carbohydrate intake is indicated. Pemberton has produced considerable evidence suggesting that the arthritic does not utilize sugars and starches to best advantage. Moreover, the gastro-intestinal tract itself, usually functioning subnormally in these patients, should not be subjected to the extra burden of an excessive carbohydrate intake. The digestive apparatus should be considered as one of the important systems which must be adjusted to its optimum functional level in our efforts to restore the patient's "physiological equilibrium." For diet lists, with a critical discussion of the entire subject, the reader is referred to Pemberton's book.<sup>2</sup>

Constipation as a concomitant symptom is almost the rule in arthritis. The practice of occasionally placing these patients on a twenty-four-hour diet of orange juice and magnesium sulphate brings with it prompt alleviation of symptoms. This may be done by giving the patient 1 ounce of magnesium sulphate in a glass of hot water flavored with lemon juice on rising. A glass of milk is provided in place of the three daily meals. One tablespoonful of mineral oil with 1 teaspoonful of the fluid extract of cascara may be given once or twice daily

to regulate the bowels, the cascara being quickly cut down or withdrawn within a few days. The use of hot wet abdominal packs after meals will help in promoting better absorption, and this procedure, in conjunction with 5 units of insulin before meals, may bring about a gain in weight in undernourished individuals with poor appetite. The insulin may be increased 5 units a day until 20 units are given before each meal.

The feeding of extra calories between meals in the form of milk shakes or egg-nogs has benefited many. Vitamins have been advocated in various forms. Responsible workers in the field have urged the use of vitamin B in arthritis, others have emphasized the value of vitamin C, and still others, with equal authority, have urged that vitamin D be administered in large quantities. Cod liver oil appears to retain its original merit, and is favored by most investigators, either in liquid or tablet form, over the numerous proprietary vitamin products on the market. It should be taken regularly by arthritics, especially during the winter months. Milk, containing as it does all of the vitamins, may be included with profit in the dietary of every patient.

Weight-reducing diets are of the first importance in the treatment of osteo-arthritis, where the weight-bearing joints are implicated. A sharp loss in weight may be the only effective means of securing definite relief from symptoms.

5. **Vaccines.**—In the home treatment of chronic arthritis, it is quite possible to carry on a course of vaccine therapy, injections being given once a week. If the attending physician will consider the vaccine an adjunct to the program which he has instituted, I would favor the use of vaccines in selected cases. It should be avoided in acute forms of the disease, unless very small doses are used. The lack of uniformity in dosage, organism selected, as well as method of application, that is, subcutaneously, intramuscularly, or intravenously, suggests that investigators have not yet found a common ground on which to meet as far as vaccine therapy is concerned with arthritis. Recent work by Dawson lends additional support to the theory of a streptococcal factor which may yet prove an

important element in the etiology of the disease, but until more conclusive evidence is at hand, we should not allow ourselves to be carried away with the idea that any form of vaccine therapy is of genuine merit. I personally favor small doses of a mixed streptococcus vaccine by the intravenous route, starting with 50,000 to 100,000 organisms, always endeavoring to keep below a reaction dose.

Foreign proteins are of extremely limited value in chronic arthritis. In gonorrheal arthritis they may occasionally be useful by reason of the increased temperature produced. For this purpose typhoid vaccine appears to be as effective as any, starting with 25,000,000 organisms intravenously, increasing by a like amount at intervals of four days, within the limits of the patient's tolerance.

**6. Occupational Therapy.**—It does not follow that enforced rest means enforced idleness. The arthritic patient should be encouraged to engage in some form of productive work which will serve the double purpose of providing mental stimulation and exercise for the affected joint. If the patient can produce some bit of work, however trivial, he will have the incentive to go on to further achievement. Knitting, painting, woodwork, modeling, braiding, making hooked rugs, dominoes, cards, and other games may be the means of restoring self-confidence and promoting greater independence.

**7. Drugs.**—Most of the common drugs and many of the unusual ones have been advocated for the treatment of arthritis. Patent medicines have thrived and are thriving today on an unsuspecting arthritic public. Very few drugs have stood the test of time. The salicylates, arsenic, potassium iodide, and iron have a definite place in the drug therapy of arthritis. The salicylates should not be employed for indefinite periods, indeed, it is usually possible to decrease dosage rapidly, omitting the drug entirely as the patient approached a more stable functional balance. To depend on salicylates as a primary agent in controlling the disease is to court disaster. Arsenic in small quantities is useful as a tonic and tissue stimulant in those individuals debilitated through long standing illness. It



may be given in the form of Fowler's solution in gradually increasing amounts, in the form of sodium cacodylate  $\frac{1}{12}$  to  $\frac{1}{4}$  grain three times a day, or intravenously, as it is used in antiluetic therapy. In the latter case, a vacation should be permitted after 6 injections. Potassium iodide, 5 drops in water three times daily, increasing to 10, often exerts a favorable influence on metabolism. Iron is frequently essential in controlling the secondary anemias so common in arthritis. Feosol is a suitable preparation for this purpose.

Opiates should never be used, except in emergencies. Suspect malignancy in the patient with arthritis whose pain requires the prolonged administration of opiates.

Cinchophen has no special merit in chronic arthritis.

Very recently hormone preparations have been used with some success, and it is likely that this field offers more for the future. An example in point is the use of the follicular ovarian hormone hypodermically for the relief of symptoms associated with menopausal arthritis or "arthralgia," particularly when vasomotor disturbances and menstrual irregularities are present. Thyroid substance in small doses may be used with discretion, more especially in osteo-arthritis, where it is thought to be most effective.

The best to be said concerning a host of other drugs is that occasionally someone appears to derive benefit for reasons which cannot be explained. Students of the subject agree in general that the place of drug therapy in arthritis is exceedingly limited, and any treatment of this nature cannot hope to compensate for the absence of a fundamental program upon which all forms of special treatment should rest.

§ **Psychotherapy.**—Worry, anxiety, fear, and other emotional states exert a deleterious influence upon the course of chronic arthritis. The patient's family and friends can help materially by cultivating his self-confidence and turning his thoughts to those things which point to progress and returning health. The clergy may do much in this regard, and their services should be sought as occasion demands.

I cannot emphasize too strongly the important share that

a spirit of continued optimism and friendly encouragement on the part of the physician may take in effecting satisfactory progress on the part of the patient. Too many patients have been disappointed and chagrined to discover that the doctor who would take a genuine personal interest in their arthritis was not to be found. Haphazard guess work in one direction or another inevitably leads to disappointment all around.

The physician who proceeds along the outlines suggested in this paper will find himself able to talk with his patients with confidence and assurance based upon results that cannot be discounted.

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## CLINIC OF DR. BRONSON CROTHERS

### THE CHILDREN'S HOSPITAL

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#### THE PRACTITIONER'S RESPONSIBILITY TOWARD THE NERVOUS CHILD

MENTAL hygiene, with or without capitals and quotation marks, has been discussed inside and outside of the medical profession for about twenty-five years. During the same period extramural psychiatrists have gained a valid place for themselves as indispensable practitioners in large communities. Psychiatric social service workers, psychologists, visiting teachers, visiting nurses and, more recently, various official groups under government auspices, are dealing with many problems which, if handled at all, used to be regarded as responsibilities of doctors in general.

Those physicians who deal with children, whether as pediatricians or as general practitioners, have taken a very small part in the discussions. Yet one of the major aims of the most vigorous of the various groups has been the prevention of mental disease by judicious management of children and of the teachers and parents who control them.

The slogan "mental disease is preventable, mental health is procurable" happens to be the one that recurrently faces doctors in this community who open their mail conscientiously. If this is true, it is evidently the duty of doctors at large to make a sincere effort to understand and to cooperate. Otherwise they will be forced to share the sense of guilt which oppresses those who should have foreseen and averted disaster. If the slogan is not correct they are in a position to comfort many distressed parents whose children have not achieved satisfaction when they began to compete in the world.

A very complicated and serious situation exists when the practitioner is asked to advise parents whose children's behavior is not satisfactory. The fact is evident enough that the ordinary methods of medical practice are almost irrelevant. The doctor is tempted to apply the definitive, episodic observations which are so useful in ordinary practice, to the problem of behavior. He is then in the rather absurd position of advising about treatment when he has no direct knowledge of the condition he is discussing. This situation strikes me as an extremely important one, particularly if we intend to try to "prevent mental disease." At the risk of repeating perfectly obvious platitudes a few remarks seem in order about medicine in general.

In ordinary medical practice among adults the history is obtained by a series of questions and answers. Some of the primary ones are aimed at the establishment of a date on which the patient was in normal health. This basic point is set at a time when the individual was at work without distress, was at a proper weight and enjoyed himself at meals and at play. The assumption is made that this evidence justifies the statement that the individual was a well-standardized product. The disease then occurred and the patient departed from his normal state of health and fell into a state of illness. The nature of the deficit in weight, in comfort, in motor ability and in mental efficiency is then inquired into, and the physician proceeds to investigate the physical status and perhaps calls upon a laboratory to investigate phases which elude the eyes, the ears and the fingers.

In children the situation is modified, of course, by the fact that steady growth is going on. It is therefore less easy to establish a base line, but since most of the diseases of children are acute, the difficulty is not too great. One of the major difficulties is evident enough in prolonged illness. Recovery in an adult is restoration to a previously achieved level. If an adult is as "good as ever" the doctor agrees that all is well. If, however, a child has been ill and at the end of six months is where he was to start with, he is suffering from "ar-

rest of development." Evidence of restoration to a proper rate of growth and development is obviously one of the things that we need before we dismiss a child after serious illness.

The problem which faces anyone who tries to deal wisely with children whose behavior is unsatisfactory cannot be dealt with by the medical routine unless the doctor is willing to shift his emphasis to a very considerable extent. It seems quite clear that the history must be taken in a very different way and that the physical study is likely to take a secondary part. The precise methods of the laboratory are likely to be even less important. Moreover the physiological study of the physical machine is less apt to reveal significant clues than a study of the behavior of the child.

It is at this point that the practitioners of organic medicine and the psychiatrists are likely to arrive at an impasse. The psychiatrist is very rarely faced by the problems of fever, pain or malnutrition, which make up the bulk of the presenting symptoms in pediatrics. Most of his patients are physically in fair condition. As a result the psychiatrist can afford to spend time in almost unlimited measure in interviewing parents or observing children, while the general practitioner or the pediatrician is accustomed to reach a conclusion at once. This sense of time has, I think, more importance than most of us realize. The statement, which is so frequently made, that the general practitioner has "not time," has been regarded with impatience or incredulity by the propagandist who advises doctors in general to deal with problems of behavior.

At this hospital we have been trying to find out whether we can work effectively with behavior problems within the time limit which is acceptable in pediatric practice. Furthermore, we have been exploring the possibility of appraising emotional and intellectual difficulties which occur in sick children before they can be released from medical supervision. At present we are dealing, in large measure, with children whose difficulties of behavior seem too confusing to be soluble in the general medical out-patient department or with those whose physical status demands ward care.

We have arranged the time of interns and of the rest of the staff so that it is possible to take histories at leisure. Furthermore, the senior members of the staff regard the history with interest and frequently cooperate in collecting it. The questions relating to growth and development are carefully considered and the mental status is considered by the psychologist who works in the ward. In addition to a careful psychological study of the child, she interviews the parents and collects relevant information about the developmental history and the educational status.

Every pediatrician knows only too well that it is difficult to appraise emphasis in histories or even to elicit facts from an anxious mother who is distressed by the behavior of a child. Too often the physician makes a guess and decides to proceed on the theory that the child is being mismanaged. A large number of well-informed and conscientious women are all prepared to accept this decision and are eager to apply remedies. Of course, there are plenty of situations where experienced doctors can help oversolicitous mothers by routine advice. On the other hand we, at this hospital, have serious doubts concerning the validity of the sort of advice which is frequently given if it is not preceded by adequate observation.

In many cases it seems wise to insist on a chance to observe the child before laying down the law. Fortunately we have a corner of the hospital at our disposal where we can watch children in action. Beds do not fill all the space. There is room for play and for teachers, so that relevant observation is possible. In addition we have medical and psychological supervision, but the essential point for the purpose of this clinic is that the behavior of children is subject to observation. The amount of space available here is liberal because we happened to be lucky in formulating plans just at the moment when generous supporters were ready and able to help us. Without this support we would have had to find space as we could. However, it is not essential to duplicate this plant before starting the investigation of behavior as an element in the study of medical cases. The fitting of a new enterprise into hospital

space is largely solved when trustees and staff agree that effectiveness of service can be increased by providing the new service.

The essential shift is one of medical emphasis. The decision to accept behavior of children as a phenomenon to be studied in a hospital means that psychological investigation must be provided for, that contact with teachers must be arranged and that time and space must be sought. It is not easy to make adequate adjustments, but without such adjustments there is not much use in starting. Frequently it is entirely reasonable to seek cooperation with existing agencies, so that a fully equipped staff is not needed.

Obviously the experienced practitioner, after watching a competent unit, gains the same type of competence in choosing cases which should be referred to psychiatrists that he acquires by watching skilful surgeons or other specialists in a highly organized environment.

The general method used in the ward can be easily described by showing cases.

Case I.—A Jewish girl of six and one-half years was brought to the hospital after being excluded from school for tantrums and impertinence. The exclusion from school was not the result of an impulsive act on the part of an angry teacher, but was forced by a succession of overt acts which upset school routine and the procedure was advised by a highly competent visitor. The mother struck us all as a very difficult, harassed woman who was trying to fight her way out of an almost impossible situation. It seemed unlikely that we would be able to accomplish much unless we did two things. First, it seemed essential to remove the child from home and second to investigate the behavior of the child ourselves. After some backing and filling, we succeeded in having the child admitted. The general attitude of the mother was that the child was an attractive, lovable little thing whose acquaintances sought her companionship. She admitted under pressure that she was capricious in her eating, slept poorly and did not behave well in school. Clearly, she wished to give the impression that she blamed the school and she expected us to support her.

The physical study was essentially negative except for strabismus. The ordinary psychometric studies confirmed those done in school which indicated that the intelligence level was above the average. She had no intellectual peculiarities which would explain resistance or unhappiness at school. The few days in the hospital were interesting from several points of view. First, the child although she sought attention and responded to it, was not at all unmanageable. She conversed freely and it was on the basis of her conversa-

tion that we were able to discuss previous management with the mother. It required some care to avoid breaking faith and at the same time to use all relevant material, but before we got through it was possible to be entirely frank all around. Second, the mother lost most of her combative attitude and was able to discuss her management and to argue about changing her methods. Third, through cooperation with school system it was possible to avoid a situation where a teacher was forced to readmit a child she had dismissed. These arrangements were made, not by us, at the hospital, but by school authorities.

In this case we were, of course, using rather formidable machinery and were cooperating with a large school system. The success of the effort, which we have followed for many months, is due, I believe, to a type of cooperation between doctors, teachers and psychologists, which can be used over and over. The school and the home had clashed. A child, perfectly capable of orderly school progress, had been removed from school. As so often happens the medical profession was called upon to intervene, not because doctors, as such, are particularly informed upon the matters at issue, but because the traditional prestige of medicine was valuable. The main reason our intervention worked well was, I think, that we were given an opportunity to observe the child during a period when parental wrath was cooling off.

Case II.—A cheerful little girl of two years and eight months was brought to the hospital because the mother was troubled by persistent head banging at night. She sucked her fingers, she had to be urged before she would eat a diet which satisfied her mother. Even under the rather difficult conditions of the out-patient clinic the child was extremely active and both the young and active parents were watching her and were all set to start after her whenever she began to move. The upshot of a reasonably leisurely interview was the rather obvious conclusion that the child was physically adequate, extremely restless and not feeble-minded. We had, of course, no direct evidence whatever as to the head-banging episodes or other things that were reported. The question arose at once as to the advisability of admission of such a child for study. The parents seemed to be in a good physical state and, though rather anxious, did not seem exhausted. Obviously they were overstating the case when they said they had hardly slept at all for months. It was a temptation to impress them with the fact that they were oversolicitous about a healthy child, give them a fight talk about judicious neglect and a suitable routine and pass on to the next case. Another possibility was to acknowledge the need of study, but to call upon a psychiatric unit to conduct it.

The quick, rather unpredictable activity of the child suggested the un-



inhibited behavior of children after cerebral injury or encephalitis. We have frequently seen management fail in such cases, and mothers battered in the process. In order to lay a foundation for advice the child was admitted. The physical study revealed no evidence of organic disease. The psychologist was not able to conduct an orderly test at one sitting on account of the restlessness of the child, but had enough evidence to suggest a developmental status between two and two and one-half years. The nurse's notes, the nursery school teacher's notes and the repeated episodic observation of the rest of the staff impressed us with the essential accuracy of the general story by the mother. It happened that the things we saw were not identical with those reported. For instance, head banging at night was not noted, but the child did a lot of rocking in chairs and on playthings and showed her passion for repetitive rhythmic activity. No conventional masturbation was observed. She was persistently restless and overactive and no routine modified the situation. Careful consideration of the home routine convinced us that no change in management would transform the picture.

At the end of a few days we were able to talk intelligently with a mother who was rested enough to discuss matters calmly and go over the very difficult problem that faced her. We were able to reassure her about her own competence and the whole situation, though still very difficult, was handled with reasonable security on both sides. At the very least we avoided the frustration which must have ensued if we had impressed her with the entirely unjustified idea that she could modify management and obtain an orderly and docile child in short order. At subsequent visits we were able to deal with the recurrent problems with confidence since we had the background obtained by direct observation. To some extent it is now possible to discuss with the mother and father shifts of procedure and attitude which might be tried. All of us, I think, are quite convinced that a few days' observation saved many hours of rather confused and unsatisfactory speculation in the out-patient department.

**Case III.**—A girl of seventeen months was brought to the out-patient department with a story of convulsive attacks at long intervals since she was ten months old. The history suggested that her development was a bit retarded and she was decidedly small for her age. Without direct observation the diagnosis of epilepsy in an undernourished and perhaps feeble-minded child had something in its favor. Certainly the initial story suggested some such situation.

On admission we discussed the problem at leisure and found that the mother had worried about management all the time. Food habits, discipline and inadequate behavior were worrying her, entirely aside from the startling episodes of crying, cyanosis and weakness which had been interpreted as convulsive attacks.

The child spent a month in the hospital. The strictly structural study revealed a few evidence of interference with growth, presumably due to nutritional disturbances, which were described by the mother. Otherwise nothing of importance was found. The regulation of her food habits by allowing her to eat her favored but suitable diet was successful from the start. We used the method which Dr. Clara Davis has so adequately proved at the Memorial

Hospital in Chicago. The summary of the nursing notes is given to show the general situation:

*Nurse's Notes.*—"Sept. 10: Pale, slender baby who has no obvious abnormalities was admitted with temperature of 100° F. She ate a moderate amount of supper—pabulum, fruit, drank milk from cup. Slept fairly well.

"Sept. 11: Listless and sick. Took cold fluids, but refused solids. Went for x-rays.

"Sept. 12: Much better this A. M. Ate her breakfast well, watched children in Nursery School. Pointed to pictures of dog and boy and handled small toys. Is a listless and apathetic baby. She stands and walks with slight support. She refused all her dinner and ate her supper well. Evidently prefers cereal and fruit meals to meat and vegetable meals.

"Sept. 13: Crept a little, sitting down. Appears weak and sickly, rather than stupid.

"Sept. 14: Feeding difficulties more obvious. Does not wish dinner food. Seems more vigorous. She uses a few words, uses toilet sometimes and refuses to other times and screams.

"Sept. 16: Started on self-selected diet.

"Sept. 18: More vigorous and active and less willing just to look on. Puts pegs in holes, looks at pictures and moves around with vigor. Likes to walk with one hand support. Says 'Thank you,' 'doggie,' 'daddy.'

"Sept. 22: Using spoon well, but makes no attempt to hold cup yet. Attitude toward meals good and she is always ready for them. Stiffens and trembles at a sharp noise. She doesn't seem to be of convulsive nature, but more just very sensitive. Plays with the other children and is gaining in strength and abilities steadily.

"Sept. 24: When her shoes were put on, she said 'shoes' after me as I said 'new shoes.' She is walking much better with the shoes on.

"Sept. 25: Viosterol started and taken well on a bit of cracker. She cries in her sleep occasionally and chews on fingers, but is teething.

"Sept. 28: Threw sand about and tried to imitate the other children in making sand cakes.

"Sept. 29: Now walks alone pushing light doll carriage.

"Sept. 30: Social with everyone now. She greets us in the morning with a grin and 'Hi.' She uses more words—'dollie, doggie, shoes, socks, nice, all-gone.' She loves to be played with and is determined and easily made mad when she doesn't achieve desired end promptly. Bowels loose.

"Oct. 1: She was yelling to go to the dining room table at 7.30 A. M. She has a slight cold.

"Oct. 3: She handles her cup if it is only one-half full and she continues to progress toward independent walking. She tries to stand alone from a sitting position, but the floor is too slippery. She walks with whoever will loan her a finger.

"Oct. 5: Uses kiddie car effectively outside and rode herself to the sandbox where she started digging. Today she stands entirely unaided. She is taken off the self-selective diet as it seems no longer necessary and she has the ordinary diet. She still has some coryza; she is not sick, but emotionally unstable, cries and is petulant when she has to wait or is crossed.

"Oct. 9: She is happy, talking and laughing. She eats with a good appetite and handles her spoon well for her age. Her cup is taken well but is supported only if one-half full. Her vocabulary is increasing and is very near to entirely independent talking. She is not reliable in bowel and bladder control and makes no effort to tell her toilet wants (training has been erratic at best). She is easily startled and upset, but nothing of the nature of a convulsion has been observed. Discharged home."

The summary of the psychologist's notes indicates the field of inquiry as well as the results of more technical tests.

*Psychologist's Notes.*—"Mother 'waited five years for a baby.' As she was too ill to nurse the baby, the grandmother took care of G. until the child was three months old. The mother consequently felt insecure about feedings from the beginning. At six months G. refused solid foods, couldn't take Cod Liver Oil. Mother tried tentatively various methods of persuading G. to eat, but without success and each meal ended with the bottle. Mother never 'had courage to let the child go more than one meal without food.' The problem was further complicated by convulsions. My impression is that the mother's anxiety developed out of a real feeding difficulty, not created by her attitude."

*Mental Tests.*—"The child does not walk alone, but she can step along supported by one hand. If left standing by her pen she soon tries. (? muscular weakness.) In general her play with test material was between 15-18 months. Her language is also up to age. According to the mother the baby used three or four words on admission and she has added a few more frequently. As she grows stronger the prevailing mood has changed. When she first came, she solemnly watched what was going on and now one often sees her laughing.

"Unusual concessions have been made to the feeding problem—the self-selective diet. The mother has watched the child eat here and was very much pleased with the result. She probably would not have had the courage to permit such a variation from the usual diet for a child, but if the child gains she may be able to carry it out at home—more particularly if she can feed herself before she leaves the hospital. The mother is not impatient to have her at home under the circumstances, but she thinks she can manage to carry out the hospital instructions without interference from other members of the family. The father is away all day and the grandmother does not live at the house."

**Summary.**—Back of these summaries are adequate records which show the steady advance. When the child was discharged we were able to do, with full honesty, several things.

1 The presumption that the reported attacks were epileptic was discredited. The probability that they represented reactive disturbances was established.

2 The feeding problem, which had produced malnutrition recognizable on physical examination, was solved and we had every reason to expect that the parents could carry on from where we left

3. The suggestion that the mental development of the child was inadequate was discredited, not by authority, but by clear evidence of advance.

4. The groundwork for a durable revision of attitude and management was laid.

On discharge it was possible to transfer the care of the child to a mother who was no longer anxious or tired. She was shown, rather than told what to do.

These cases are all recent and in none of them was an inordinate amount of time necessary to arrive at an adequate decision. Naturally they are all to be followed, but our subsequent supervision of procedure is far more confident than it would have been without a ward study.

Of course no one expects the practitioner of medicine to have a psychologist at his elbow on his rounds. The point which seems to me clear is that he should arrange matters so that he is able to form his own opinion on the nature of the phenomena which are reported to him. The man who relies on hearsay about behavior is in as weak a position as the man who relies on a telephone to interpret physical signs. Naturally it takes time and space to observe behavior, but those who feel that the study is worth while will not find the expenditure unlimited.

The 3 cases discussed do not illustrate a method of preventing mental disease. I am quite incapable of producing cases where efforts directed to such an end are in progress. It seems to me clear, however, that all three of these children were seen at a time when "maladjustment" was already evident and I believe there is reasonable ground for supposing that our intervention and continued supervision is going to improve their chances of orderly growth and development.

## CLINIC OF DR. JOSEPH GARLAND

### MASSACHUSETTS GENERAL HOSPITAL

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#### COMMON ERRORS IN PEDIATRIC DIAGNOSIS

THERE is for each of us, probably, according to our several abilities, an irreducible minimum of diagnostic errors which we will make as we go from patient to patient. Our obligation is to try to scale down to this minimum, deriving what profit we can from our errors and those of others, in order that they should not be a total loss to ourselves and to the community. It is not so important to know what errors to avoid, although this information has its value, as how best to avoid errors in general.

It may not be out of place to state, in this relation, that it is safer for the patient and one's own reputation to doubt one's diagnostic ability than to be too sure of it. To be over-sure invites a carelessness in our stewardship of other individuals' lives and welfare that may be fatal. The unconfident and unassured physician who ponders overmuch about his cases and calls often for help may not arouse our admiration, but unless he is completely paralyzed by indecision he does not deserve our contempt. Indeed, the patient is safer in his hands than in those of his colleague with an Hippocrates complex who questions all men's ability but his own and feels that he knows everything because he has learned nothing new. The physician whose word has for years been law to a devoted following is sometimes in danger of falling into this error—less often in a medically intellectual center than in a community where he has had to rely too completely upon his own resources.

An attempt to list all the errors in pediatric practice that

might be called common would be hopeless, and definite lessons can be learned from some of the less common ones, whether they are spectacular or otherwise. It is of greater importance to analyze the causes for making errors that should reasonably be avoided and to determine the method of their avoidance.

There are certain inescapable reasons for the fact that medicine is a scientific art rather than an exact science, and on this basis I should predicate five causes for diagnostic errors in any branch of the art, although we are at the moment dealing particularly with pediatrics.

These are in approximately the following order:

First, carelessness, which is theoretically inexcusable, but to which we are all susceptible in a degree dependent on our inherited characteristics and early training.

Second, lack of available knowledge, which is frequently excusable but not below a varying, moderate level.

Third, lack of an innate or painstakingly acquired ability to draw on the knowledge which we possess and to place the correct interpretation on the information which we have elicited—and to a greater or less degree we all have our intellectual blind spots.

Fourth, lack of accessory diagnostic facilities that under certain conditions may be beyond our power to obtain. We should, however, at least know those that are necessary or desirable to employ in a given case, under which conditions the correct diagnosis should be suspected even if it cannot at the moment be confirmed, and

Fifth, the other unpredictable human factor; the patient himself with his individual characteristics, his heredity and his environmental influences; in other words, the factors that make him react in his own way to the conditions that have been imposed upon him.

It is necessary, therefore, if we are to reduce our mistakes to a minimum, to take a reasonably exact and sufficiently complete history, depending on how complicated the case is and how obscure the diagnosis, as well as the importance of the

decisions contingent upon the diagnosis. Very little history is necessary in making a diagnosis of acute tonsillitis, but much more is needed in deciding on the advisability of a tonsillectomy or the possible presence of a rheumatic infection. It must be remembered that in pediatrics the historical data are objective rather than subjective; the facts are usually derived wholly or in part through an interested third party.

The physical examination should be carefully, even if rapidly, made under all circumstances, for no physician can afford, because a given diagnosis is simply made, to run the risk of overlooking a complication or a coexisting pathologic condition. While routine methods are always desirable, it is often necessary, in dealing with young children, to elicit physical data in an apparently haphazard order, selecting the easiest and most casual approach to a difficult patient. The most disturbing examinations, usually those of the ears and throat, which are also the most diagnostically fruitful, should be reserved for the grand and often tempestuous climax.

It is not my province or purpose and should certainly be superfluous to attempt to describe the physical examination of a child. Examination of the ears, however, deserves emphasis and the physician who assumes the care of children should have the necessary equipment and training to undertake this examination. Too often we find that the diagnosis of acute otitis media has been first made when the ears begin to drain. We may assume that the mouth and throat are usually inspected, but frequently the presence of a cervical adenitis is overlooked with disastrous results so far as diagnostic accuracy is concerned.

One of our medical Nestors said on a certain occasion that the chief functions of a consultant are to make a rectal examination and console the family of the patient. The rectal examination is not so often essential in pediatrics as it is in internal medicine or in surgery, but it is always indicated in rectal bleeding, which may be due to polyps, piles, or fissures, or where a surgical abdominal condition is suspected.

Many of the peculiarities of the human mind and body

are still beyond the range of any knowledge, but nevertheless a vast reservoir of available information exists that is being constantly added to, corrected and brought up to date. No one has all of this material, even in his chosen field, at his immediate command. The able pediatric consultant should be at least familiar with the bulk of the practical knowledge in his specialty; the practicing pediatrician should know much of it and should know something about most of the rest; the general practitioner may be excused for a considerable degree of ignorance about much of the specialized data, but should have a working knowledge of the common conditions of childhood and a general idea of the principles of pediatric practice.

More than a fund of knowledge, however, is necessary in the practice of medicine. There must be the ability to cerebrate along the lines of that knowledge, coordinating it with the information that has been gained by careful observation. To the born physician this is very nearly instinctive; the rest of us must acquire it through patience, perseverance and rigid mental discipline. It once was said of a well-known physician that his analyses of cases were marvels of logical deduction, but his chief value as a consultant was that the patient never had the disease he selected; his conclusions were always wrong. He had knowledge and industry, but no ability to combine the two, and knowledge without a certain amount of wisdom is a motor without a spark.

An excited practitioner brought a patient on the verge of tetanic convulsions to our hospital not many years ago. "Day before yesterday," he said, "this man complained of stiffness of the jaws. Yesterday it was worse. This morning it was still worse and he said to me, 'Doctor, do you suppose I have lockjaw?' 'Great Scott,' I said, 'why didn't you mention that before? I never thought of it!'"

Laboratory facilities have become a recognized part of our modern diagnostic armamentarium, and the patient has a right to their aid when they are indicated and where they are available. The doctor must decide when they are indicated, recognizing also that superfluous ones merely gild the lily and



empty the patient's pocketbook. Too often, I am afraid, necessary procedures are neglected because they are not *easily* available. There are few patients who cannot by some means be transported to a good hospital once the necessity for it is seen and acted upon, but not infrequently we encounter cases that have been wrongly diagnosed and incorrectly treated for weeks before the effort is made to procure the best service possible for them.

Even if these facilities cannot be immediately procured the physician with a reasonable amount of knowledge and a reasonable degree of wisdom will have decided upon the procedures he believes necessary to confirm the diagnosis that he is considering. He will himself, of course, have the means for making blood counts, analyzing the urine, and performing the tuberculin test.

Last, and not the least difficult, comes the appraisal of the individual who is harboring a disease the nature of which we are trying to determine, and here a knowledge of the patient and his family may be of great assistance. More information, both in the history and on the physical examination can be obtained from the cooperative and well-adjusted child than from the spoiled, resistive and emotional one. The shape of the jaws and the expression of the face may denote an abundance of adenoid tissue and a susceptibility to upper respiratory infection; body build and body mechanics may suggest the common enemy of modern childhood—chronic fatigue.

One of the commonest errors in pediatric practice is to attribute all the nutritional disturbances of infants to improper diet. Many infants are weaned from the breast or have their formulas changed from one mixture to another, from one proprietary food to the next one, when all they need is to be given enough of nearly any type of food to satisfy their hunger, or to have the environment so changed that they can live in peace within it.

Two out of 5 babies who are colicky, wakeful, unhappy and vomiting are hungry. They are being given insufficient amounts of food, usually too dilute, often in too many feedings

and frequently at too short intervals. Overfeeding or an unsuitable formula is the ready diagnosis, a diagnosis quite probably insisted upon by the mother or nurse, and the round of experiments commences, usually with a food still more highly diluted.

Two more out of the 5 are reacting strenuously to an environment which does not allow them sufficient opportunity or time to vegetate—to rest and to sleep. The baby is used either as an animated human exhibit for friends, relatives and the bridge club, or it is expected to slumber through an atmosphere charged with the high voltage of anxiety. The response is apt to reflect the results of overstimulation—hypertonicity, fatigue and reflex digestive disturbances, and the treatment usually consists of a change in formula.

The last one of the 5 may suffer from the results of a food either grossly improper for any comparable infant or specifically unsuitable for the individual. A fat or sugar intolerance will manifest itself by vomiting and diarrhea or both, with presumably failure to gain in weight, or by colic and restlessness. If adjustment of these principles does not effect an improvement, an allergic reaction to milk protein may be suspected. Gross overfeeding may cause difficulties; most infants will sensibly refuse or reject food that they do not need.

Appendicitis is a condition that has stirred both medical and popular fancy sufficiently for decades so that by now one would suppose few mistakes should be made in its diagnosis. Acute surgical conditions of the abdomen in children are notoriously uncertain in their signs and symptoms, however, and various writers have shown that a real menace attends a complacent attitude toward abdominal pain. Hudson<sup>1</sup> has pointed out that in Massachusetts between 1900 and 1930 child deaths from appendicitis have increased 428 per cent during a period in which the child population increased only 41 per cent. In 1919 the disease did not appear among the first 10 causes of death, but from 1926 to 1930 ranked eighth, and for the longer period, 1926 to 1933, occupied fifth place in the age group one to nine.

It is wise always to consider first the possibility of appendicitis when the classical triad of symptoms, abdominal pain, vomiting, and fever occurs, and to avoid any tendency to adopt a casual rather than a watchful policy of expectancy. Hudson found that pain was the most common symptom, occurring in 99 per cent of the patients observed. It may, however, be poorly localized or complained of only on micturition or defecation, and it need not be severe. Local tenderness was found in 94 per cent of these patients and the necessity of a rectal examination was emphasized.

Muscle spasm Hudson found in 83 per cent of his patients studied, but "to appreciate muscle spasm in the child, patient approach, prolonged examination and experience in the examination of children are necessary." The spasm may be of much less degree than will be found in the adult. Nausea or vomiting was noted in 92 per cent of these patients.

The fever usually ranges from 99° to 101° F. but with wide variations. In the obstructive forms of appendicitis fever may be absent. Leukocytosis is usually between 12,000 and 20,000 but again with the possibility of wide variations.

A differential diagnosis between acute appendicitis and acute mesenteric adenitis may be practically impossible to make, and, if there is doubt, operation represents the conservative decision. Inflammation of the peritoneum primarily infected, as from the pneumococcus, can rarely be distinguished from inflammation secondary to appendiceal involvement. Rheumatic fever may cause abdominal pain closely simulating an attack of appendicitis; in some cases in which laparotomy has been performed inflammation of the diaphragmatic peritoneum has been found; in others, nothing. Infections of the upper urinary tract must be excluded by examination of the urine and this should always be done where appendicitis is suspected.

It is well to bear in mind, also, that appendicitis may co-exist with or result from other infectious diseases. The incidence of appendicitis is likely to rise when upper respiratory diseases are prevalent, and Hudson and Krakower<sup>2</sup> have noted

an association with measles which is more than coincidence, reporting 8 such cases.

Pneumonia is the classical disease which, at its onset, may simulate nearly any acute infection, but particularly appendicitis and meningitis. A boy of five who was seen a few years ago had for three days been delirious with high fever, stiff neck, and a positive Kernig sign. A tentative diagnosis of meningitis was made and he was sent to the hospital, where lumbar puncture disclosed a normal spinal fluid. Four days later a patch of bronchial breathing appeared in one axilla and x-ray revealed complete consolidation of a lobe.

Adams and Berger<sup>3</sup> some time ago called attention to the frequency with which pneumonia is mistaken for appendicitis, and today nearly every pediatric house officer boasts of the occasions (perhaps largely imaginary) when he has rescued pneumonia patients from the trucks on their way to the operating amphitheater. These authors found that abdominal pain, vomiting and diarrhea occur as frequently in pneumonia as in abdominal conditions. The pneumonia patient, however, always seems more ill and shows much more of a systemic reaction as evidenced by pulse and temperature chart than does the abdominal case.

A high leukocyte count (over 20,000) favors the diagnosis of pneumonia against that of appendicitis before rupture. In pneumonia abdominal tenderness seems more severe, but less localized; "frequently the child jumps or cries as soon as the abdomen is touched, and deeper pressure does not add to the discomfort; the part affected seems superficial rather than deep, and at times almost suggests a hyperesthesia. The tenderness in the uncomplicated appendicitis case may be slight; it is always less impressive than that of a pneumonia, and is more readily localized, usually to a small area in the right lower quadrant."

When any infectious disease is prevalent in a locality, a diagnosis under consideration is more likely to fall into that group than would otherwise be the case, particularly if the epidemic disease is common and widespread. Certainly the

epidemic infection must be considered and excluded, if there is doubt, before the diagnosis is established on some other basis. Mistakes are commonly being made, however, in concluding too casually that the disease in question belongs in the prevalent group.

A dramatic or especially dreaded disease may assume undue importance in the minds of both the laity and the medical profession even if its epidemic incidence is far below that of less spectacular conditions such as the upper respiratory infections or measles. During one of our recent outbreaks of anterior poliomyelitis two respected physicians in a neighboring town decided in consultation that a certain boy had the disease. An agent of the infantile paralysis commission, called to see the case, was forced to point out as tactfully as possible that the child had an injected pharynx and acute cervical adenitis—sufficient cause for the stiff neck of which he complained. A careful physical examination and a little deductive reasoning should have been sufficient to have established this diagnosis in the first place.

Another agent of the commission, during the same epidemic season, was called to some distance in considerable haste to assist in the salvage of a paralyzed case. On arrival he found an elderly gentleman who had just sustained a cerebral hemorrhage with resulting hemiplegia!

Due to the panic incident on its arrival, no disease is suspected in so great a variety of types of infection as is infantile paralysis. Fond parents are largely responsible for this, for they see a stiff neck or a rigid back in any condition, and the lameness resulting from a stone bruise is sufficient excuse to bring the doctor out at any hour of the day or night. The amount of back raising and neck bending that healthy children are subjected to at these times is enough to give a degree of muscular lameness about the vertebral column, and the implication with which these calisthenics are associated can easily bring the rest of the symptoms to the mind of the patient.

In general, diseases of the respiratory tract and their complications lend themselves most readily to diagnostic errors.

This is due partly to inadequate examination, particularly of the pharynx, tympanic membranes and cervical lymph nodes, and partly to the great difficulty, with children, of finding and interpreting pulmonary signs. If a temperature of undetermined origin remains elevated for more than two or three days, especially if any signs of an upper respiratory infection are present, pneumonia should be suspected, regardless of a low respiratory rate and any condition of well- or ill-being of the patient. Frequently the roentgen ray will be necessary to confirm the diagnosis and frequently the diagnosis of pneumonia, if made, will be wrong.

Other pulmonary conditions of childhood, also, may tend to confuse the diagnosis; lung abscess, bronchiectasis, foreign body and tuberculosis.

To show that the diagnosis of a simple upper respiratory infection may also present peculiar difficulties, it is pertinent to refer to Wallgren's<sup>4</sup> remarks concerning the development of allergy in primary tuberculous infection. The period of incubation between the time of penetration of the tubercle bacillus and the appearance of allergy may vary, probably, from three to seven weeks. During this period a diagnosis cannot be made clinically, although if tuberculosis is suspected the bacilli may be found in gastric washings.

With the appearance of allergy, fever may develop, but this rise in temperature resembles the ordinary fever accompanying a cold, and is usually mistaken for one. It may be moderate in degree or may reach a height of 104° F. The onset may be insidious or it may begin suddenly, as in an influenza infection. The course may differ in no way from that of the familiar acute infections.

The distinguishing feature of this phenomenon is that with the appearance of allergy the tuberculin test first becomes positive, and at this stage the sensitivity to tuberculin, previously not present at all, may be greater than at any subsequent time. The delicate intracutaneous test is not necessary at this time to produce a positive reaction of considerable degree. The cutaneous Pirquet test and the percutaneous test with ointment

are sufficiently reliable to arouse the reaction. Erythema nodosum may also occur at this stage, although it is apparently much less common in this country than in Scandinavia. It may not be due to tuberculosis, but its appearance always demands a tuberculin test.

Not long ago I was asked to see, at a suburban hospital, a child suspected of having purpura haemorrhagica. This patient had had fever for the better part of a week, but all physical signs, including x-ray examination, were normal except for a typical erythema nodosum. A tuberculin test was requested but the parents withdrew the child from the institution and brought her to a Boston hospital, where she died within ten days of tuberculous meningitis.

Less common diagnostic errors than these types noted may also point a moral or at least adorn a tale. A surgical colleague went into the country to see an infant on whom a diagnosis of osteomyelitis had been made, or at least suggested. One does not commonly see scurvy in a breast-fed infant, but it happened to fulfil the diagnostic requirements in this particular case.

During a recent epidemic season an infant was sent to me with the diagnosis of poliomyelitis and presumable involvement of both legs. There was unquestionably pain in the legs when they were manipulated, but no paralysis, as the baby kept them firmly flexed on the abdomen. A short history elicited the information that this bottle-fed infant had had no orange juice for several months, and x-ray of the extremities showed typical lines of scurvy and periosteal elevation. Orange juice quickly changed the picture—a therapeutic test which is in everyone's hands.

One sees every so often typical Mongolian idiots who have been hopefully but fruitlessly fed thyroid extract under the impression that they are cretins; reference to a text will usually clarify the doubtful diagnostic points, even if an infant metabolism apparatus is not available. In convulsive cases tetany should at least be considered in infants, and lead poisoning in older children. A careful history may direct suspicion to

either of these conditions, which laboratory tests or a roentgen ray may confirm.

A citation of types or examples of errors leads inevitably to our original premise, that avoidable errors can be reduced in number only by careful histories and examinations and the employment of accessory diagnostic facilities when indicated and where available.

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### THE DIET DURING PREGNANCY AND THE NURSING PERIOD

THE last two decades have seen increasing emphasis placed upon the regulation of diet in the maintenance of health as well as in the treatment of disease. This increasing attention to nutrition has been the logical outcome of a galaxy of discoveries both in the fields of nutrition and of clinical medicine. Researches in experimental nutrition have led to a keener insight into the precise nutritional requirements of the body in such terms as total energy, protein, minerals and vitamins. In the field of medicine, a number of previously baffling diseases have been finally recognized as the result of dietary deficiencies, or defective alimentation of potentially adequate diets, or both. Thus, such varying disorders as pernicious anemia, pellagra, Korsakoff's syndrome, and the polyneuritis which develops after prolonged hyperemesis gravidarum have been shown to respond to specific dietary measures. Advances are rapidly being made in the recognition of a number of relatively commonplace "subclinical" nutritional disorders, such as mild scurvy, dental caries, nutritional anemias and edema.

The physiologic states of pregnancy and lactation make special nutritional demands upon the mother. At the same time, at least during pregnancy, alimentation is often less efficient than during the nonpregnant state. This is indicated

by the incidence of nausea and vomiting, the frequency of hypochlorhydria and constipation. The combination of these special demands with defective alimentation make meticulous attention to the diet during these periods doubly important.

In the clinical application of the science and art of nutrition to pregnancy and lactation, one should remember that a number of the standards set as requirements are to some extent arbitrary. Common sense tells us that women have had babies and have nursed them without the daily consumption of a whole quart of milk, and yet have escaped total nutritional collapse. On the other hand, inappropriate diet during pregnancy and lactation often leads to poor maternal health and not infrequently to serious consequences for mother and child.

The demands of the baby and the altered maternal metabolism during pregnancy and lactation result in such marked changes in nutritional requirements that these are not necessarily met by food habits which are optimum for a woman at reproductive rest. The average American diet, particularly that of women in the lower economic group, is often seriously deficient in a number of the essentials during these periods. While diets suitable for pregnancy and lactation are essentially normal qualitatively, the quantitative needs for total calories, protein, minerals, vitamins, and even water are considerably altered by these functions.

It will be remembered that the fetus in utero is essentially parasitic. It takes what it needs from the mother's blood stream regardless of her food intake. Thus when the maternal diet is inadequate, or even in the presence of an adequate diet, when absorption from the gastro-intestinal tract is defective, the maternal organism serves at its own expense as a buffer between the inadequate food absorbed and that taken from the maternal blood stream by the fetus. The cost to the mother in terms of demineralization, nitrogen loss and vitamin deficiency may be tremendous, with attendant serious consequences, such as dental caries, anemia, and even osteomalacia. The fetus suffers only if its immediate source of nutrition is depleted, a state of affairs which can exist only following pro-

longed and definitely harmful inadequacies in the maternal diet. Thus a restricted maternal diet can have little or no effect upon the weight of the fetus unless the restrictions are prolonged and dangerously excessive. This was well illustrated by the maintenance of average birth weights of babies in Germany during the war.

As a preliminary to a discussion of the practical aspects of prescribing a diet during pregnancy and lactation, it will be helpful to present, briefly and specifically, the altered needs for the several components of the diet which are brought about by these physiologic states. In doing this no attempt will be made to review the literature on this subject. For an exhaustive review of nutrition during pregnancy and lactation the reader is referred to the excellent summary of Garry and Stiven,<sup>1</sup> on which we shall lean heavily in the subsequent discussion.

**Energy Requirement.**—The basal metabolism of the pregnant woman has been repeatedly investigated. The results of these studies indicate that the basal rate tends to increase steadily from about the fifth or sixth month of pregnancy. Shortly before term it is about 23 per cent higher than in the nonpregnant woman. It has been shown that the basal metabolism of the pregnant woman just prior to parturition is equal to that of the mother and child taken separately three to ten days after the birth of the child.

The increased need in the quantity of food consumed during the early months of pregnancy is so slight as to be negligible. Even during the latter months of pregnancy, when the growth of the fetus is rapid, the total caloric requirements are never more than approximately 20 per cent above normal; for while the basal requirement is increased some 23 per cent this is partially offset by the diminished activity common to the third trimester. During the period of lactation there is a greater increase in the total energy requirement. This larger demand during the nursing period may be explained as follows:

- a. Sufficient fuel to meet the mother's own energy requirement.

- (b) Food equivalent in caloric value to the milk produced.  
(Twenty calories per ounce of milk produced.)
- (c) Fuel to supply the energy required to produce milk.  
(Equivalent to approximately 10 per cent of the fuel value of the milk produced.)

We feel that the caloric requirements commonly given for diets during the periods of pregnancy and lactation are often too high. Our clinic observations would suggest that further study along these lines would result in a revision downward of the so-called "standard energy requirements" for these periods. The average total energy requirement during pregnancy will be found to be from 2200 to 2600 calories; and during lactation from 2800 to 3200. Variations of these schedules will, of course, be necessary with reference to the size and activity of the woman concerned.

**Weight Gain During Pregnancy.**—A total weight gain for the period of pregnancy of from 16 to 20 pounds above normal weight for the individual is considered desirable. Provided that the retention of water is not excessive, the above represents the average loss during the first two weeks of the puerperium. Excessive weight gain during pregnancy should be avoided, for in addition to the esthetic objections, it is associated with a definitely increased incidence of dystocia, and probably also with increased incidence of toxemia. It is not yet entirely clear how much of the excessive weight gain associated with toxemia is due to water retention, although overeating and obesity would seem to play definite rôles. The ineffectiveness of dietary restrictions within safe limits in controlling the size of the baby has already been mentioned.

**Carbohydrates.**—During the past fifteen years hyperemesis gravidarum, preeclampsia and eclampsia have been attributed by various writers to disturbances in carbohydrate metabolism. While there is an increase in the total energy requirement during the later months of pregnancy, there is no conclusive evidence that carbohydrate is important other than as a source of energy during pregnancy. Although extra energy is needed during the lactating period, the concentration

of lactose in breast milk is very constant, and has been shown to be very little affected by the nature of the diet of the mother. There is some evidence to indicate that a high carbohydrate intake, during the nursing period, may tend to inhibit milk production.

**Fats and Lipoids.**—Very little is known about the metabolism of fats and lipoids during pregnancy and lactation. However, that changes occur during pregnancy involving fats and lipoids is indicated by the ease with which the level of acetone bodies is increased in the blood, the elevation of the level of blood cholesterol, and the ease with which (compensated) acidosis occurs, as indicated by the appearance of acetone bodies in the urine. Certain lipoids and fatty acids would appear to be essential to the diet at all times, as, for example, linoleic acid. Aside from its chief function as a source of energy, fat is of importance as a carrier of the fat-soluble vitamins A, D and E.

**Proteins.**—During pregnancy an increased requirement for protein is shown by the significant retention of nitrogen. Indeed, in so far as the few balance studies go, it would appear that considerably more nitrogen is retained than may be accounted for by the development of the fetus. Thus, in the studies of Macy and her coworkers,<sup>2</sup> it has been shown that with an average ingestion of 19 Gm. of nitrogen from proteins of excellent quality, there was a resultant mean net retention of 3.1 Gm. of nitrogen per day, representing a storage of 16 per cent of the nitrogen intake during the last one hundred and forty-five days of pregnancy. In this experiment, the subject's ability to retain an abundance of nitrogen was further shown by the fact that she stored 2.6 Gm. of nitrogen daily, beyond the calculated amount utilized by the developing ovum. The total observed accumulation was 446 Gm. at term. A compilation of statistics from other nitrogen balance studies gives the average daily nitrogen retention throughout pregnancy as 2.28 Gm., equivalent to the retention of 14.25 Gm. of protein daily. The authors state that from comparison of the two sets of data, it would seem that, in general, the richer

the diet in protein of good biological value, such as from milk and its products, the greater was the persistent storage of nitrogen during pregnancy. From their continued metabolic studies during a large part of the reproductive cycle, Macy and her associates have also shown that in some multiparae there is negative nitrogen balance during early lactation. It is also interesting to note that these women who were on high protein intakes gave high milk yields during the nursing period. It has long been known, in the dairy industry, that a high protein diet begun late in gestation in cows improves their milk yield. Other workers have also drawn attention to the fact that in women the greater the retention of nitrogen in the latter part of pregnancy, the greater the likelihood that there will be a sufficient milk supply. Certainly there is adequate experimental as well as clinical data to substantiate the idea that there is increased need for protein, particularly during the latter part of pregnancy and during lactation.

There has been a general impression that the toxemias of pregnancy are related to the protein in the diet. For this reason many obstetricians have restricted the protein intake during pregnancy. According to some investigators, toxic substances which may be harmful are formed in the breaking down of proteins, especially meat protein. On the other hand, in a recent paper Strauss<sup>3</sup> suggests that a diet low in protein may be the cause of toxemia, and he reports cases successfully treated with high protein diets. These diets were supplemented by vitamin B and liver. Certainly there is no satisfactory evidence that a liberal protein intake during pregnancy is the cause of toxemia in normal women. On the other hand marked restriction of protein over prolonged periods during pregnancy and lactation may result in diminished serum proteins with attendant edema, negative nitrogen balance, and indirectly, anemia.

An optimal intake of protein during pregnancy is approximately 100 Gm. per day. The League of Nations Technical Commission gives 2 Gm. per kilogram of body weight as a desirable intake. Animal proteins, because they are rich in

the essential amino acids should be emphasized. If the daily diet contains 1 quart of milk, a liberal serving of meat, and an egg, together with the amount of protein in the other foods of a well-balanced diet, the mother's need should be well covered. During the period of lactation protein is utilized in the production of milk, and a high protein intake is known to favor milk production. The optimum daily intake during lactation should be approximately 125 Gm. of protein of good biological value.

**Minerals.**—The 3 minerals, calcium, phosphorus and iron, which require special attention in the normal diet, need added emphasis during the periods of pregnancy and lactation. In goiter zones iodine also requires attention.

**Calcium and Phosphorus.**—The demand for calcium and phosphorus during both the periods of pregnancy and lactation is approximately doubled. During the first trimester of pregnancy this increased need is slight. By the fourth month, however, calcium and phosphorus are being deposited in most of the bones of the fetus, and the teeth are forming. All of the temporary teeth are formed during the prenatal period. The deposition of calcium and phosphorus in the fetus is greatest in the third trimester of gestation.

Not only are the amounts of calcium and phosphorus in the diet important, but their utilization is intimately related to the ratio of Ca:P, as well as to the vitamin D intake. If vitamin D is administered in very large amounts, a significantly greater proportion of the ingested calcium and phosphorus are retained by the body. Thus, a high intake of vitamin D may materially reduce the needed intake of calcium and phosphorus. However, until the physiologic responses to excessive amounts of vitamin D are better understood, some caution should be exercised in its use. Inadequacy or maladjustment of these factors during pregnancy and lactation may result in such conditions as dental decay, osteoporosis and rickets.

The results of metabolism studies, during pregnancy and lactation indicate that a higher intake of calcium and phos-

phorus than that of most women favors retention of calcium and phosphorus both in the mother and fetus. During pregnancy an intake of at least 1 to 1.5 Gm. of calcium daily, and about 1.5 to 2 Gm. of phosphorus seem advisable. The requirements for both calcium and phosphorus during lactation are probably even higher. Since milk is our best food source of calcium, it should be used liberally in the diet throughout these periods. Cheese, with the exception of cottage cheese, is also an excellent source. In general, the vegetables and fruits are good sources of calcium, adding materially to the calcium content of the diet, when taken in liberal amounts. Phosphorus is more widely distributed in foods than is calcium, and so is less apt to be deficient in the average diet. If the diet is liberally supplied with protein, as already suggested, the phosphorus needs during pregnancy and lactation will be well met.

*Iron.*—During pregnancy and lactation the iron requirement is increased at least 20 per cent. Considering the adult's normal daily requirement for iron as 15 mg., there should be at least 18 mg. in the diet of the pregnant and lactating woman. This amount of iron is necessary during pregnancy to prevent anemia in the mother. The fetus abstracts considerable iron from the maternal blood both for maintenance of a normal hemoglobin level in its blood, and for iron storage in its liver. This iron stored during later intra-uterine life serves as a reserve during the early months of extra-uterine existence, when milk, which is poor in iron, is the major food of the baby's diet. The White House Conference publication, "Nutrition," states that the child at birth has in its body 375 mg. of iron, which it has secured by daily transfer from the mother: this is said to be brought about by a transfer of about 0.4 mg. daily during the early part of pregnancy, and 4.7 mg. daily during the third trimester. This large drain upon the mother, especially in the latter part of pregnancy, together with diets often inadequately supplied with iron-rich foods may account in part, for the microcytic hypochromic anemias so commonly found in pregnancy. The diet should, therefore, be liberally



supplied with iron-rich foods throughout this period. The foods richest in iron are liver, kidney, lean meat, egg yolk, apricots, prunes, peaches, green leafy vegetables, and molasses. The whole grain breads and cereals are good sources of iron. In considering the iron-rich foods one should bear in mind the fact that certain foods are superior to others in their power to build hemoglobin, and that this is not necessarily dependent upon their iron content. Liver, kidney, apricots and peaches illustrate this fact; liver and kidney being superior to lean meat, and apricots and peaches superior to spinach. In addition to a liberal use of foods rich in iron, the authors recommend that patients be given moderate doses of iron during pregnancy (as, for example, ferrous sulphate, 3 grains three times a day).

*Other Minerals.*—In those regions where goiter is not endemic an adequate amount of iodine is obtained from the local water and foods when a well-balanced diet is eaten. The other minerals required do not usually need special attention. Salt (NaCl) sometimes needs restriction in the latter months of pregnancy if weight gain is accompanied by edema.

*Water.*—An adequate amount of water should be taken daily during pregnancy and lactation. A liberal fluid intake aids in the digestion and absorption of food and helps to prevent constipation. Liberal water intake also is of considerable prophylactic value in the prevention of pyelitis. During the early part of pregnancy an intake of from 6 to 8 glasses of water daily is usually well tolerated, but during the last trimester, especially when edema occurs, restriction of fluid intake may be advisable.

Cellulose is necessary for normal intestinal function. It is also of benefit to satisfy appetite where calorie intake is restricted. A sufficient quantity of cellulose is obtained when vegetables, fruit, and whole grain products are included liberally in the diet. However, the indiscriminate use of large quantities of roughage, such as bran, not infrequently results in troublesome intestinal irritability.

*Vitamins.*—Vitamin A is essential for normal growth and

development, as well as for reproduction. Deficiency is manifested pathologically by keratinization of the body epithelia with resultant increased susceptibility to infection. There is some clinical evidence that a lack of vitamin A in early pregnancy may cause resorption of the fetus, or later increase the incidence of premature or still births. It is also possible that there may be some relationship between vitamin A and the incidence of puerperal sepsis. While the body has the ability to store vitamin A in relatively large quantities, the demand for this vitamin during the reproductive period is greatly increased, and unless the diet includes a liberal amount deficiency may develop. The best food sources of vitamin A are whole milk, cream, butter, cheese, egg yolk, leafy green and yellow vegetables. Since vitamin A is fat-soluble, the practice of using skim milk to control weight gain during pregnancy greatly reduces the vitamin A content of the diet. If it becomes necessary to skim the milk or reduce the amount of butter in the normal diet of pregnancy, some adequate supplementary source of vitamin A should be supplied. Cod liver and halibut liver oils are concentrated sources of this vitamin as well as of vitamin D, and may be used. A diet high in vitamin A is desirable during the nursing period, since there is evidence that a direct relationship exists between the vitamin A content of the mother's diet and that of her milk.

*Vitamin B* ( $B_1$ ) in adequate amounts stimulates appetite and growth and is necessary for normal reproduction. When insufficiently supplied it may result in impaired neuromuscular control of the intestinal tract, often resulting in atonic constipation. Deficiency of vitamin B ( $B_1$ ) is an important secondary factor in hyperemesis gravidarum; in some prolonged and severe cases it would appear to contribute to the so-called "polyneuritis" of pregnancy. Foods rich in vitamin B ( $B_1$ ) are whole grain products, vegetables, fruits, milk and egg yolk. Brewer's yeast and wheat germ are concentrated sources and can be used when additional vitamin B ( $B_1$ ) is needed. The requirement for vitamin B ( $B_1$ ) is high during both pregnancy and lactation. The vitamin B ( $B_1$ ) content of breast milk is

largely dependent upon the vitamin B ( $B_1$ ) content of the mother's diet. Metabolism studies indicate that from three to five times as much vitamin B ( $B_1$ ) is necessary for lactation as for normal growth and maintenance. The increased requirement is probably nearly as great during pregnancy itself.

*Vitamin G* ( $B_2$ ) is found in many of the foods rich also in vitamin B ( $B_1$ ). Meat and milk contain more vitamin G ( $B_2$ ) than B ( $B_1$ ). If the diet is well supplied with meat and milk it will not be deficient in vitamin G ( $B_2$ ). Deficiency of vitamin G ( $B_2$ ) results in lack of vigor and premature senility. Pronounced deficiencies are associated with the etiology of pellagra and a type of macrocytic hyperchromic anemia. Pregnancy and lactation increase the need for this vitamin as is suggested by the observation that latent pellagra may become manifest during these periods. Furthermore, certain cases of macrocytic hyperchromic anemia during pregnancy respond promptly to the exhibition of this vitamin.

*Vitamin C*.—The requirement for this vitamin is increased both during pregnancy and lactation. In experimental work with guinea-pigs, on diets very deficient in vitamin C, the female does not conceive because of failure of ovulation. When the deficiency is less marked, abortion or resorption of the fetus takes place. The young of scorbutic does show signs of scurvy. Evidence of suboptimal intake of this vitamin among women is often seen in the condition of the teeth and gums. It also plays an important part in the bone and tooth development of the baby. Extreme deficiency results in scurvy. The diet should contain one or more excellent sources of vitamin C daily. Citrus fruits and tomatoes (raw or canned) are excellent sources. In using tomato juice instead of orange juice it takes at least twice as much of the former to give the same relative amount of vitamin C. Raw cabbage is also an excellent and inexpensive source of this vitamin.

*Vitamin D*.—As has been stated vitamin D in adequate amounts is important in promoting optimal utilization of calcium and phosphorus. Vitamin D has few good food sources. The best food oils are our best natural sources of this vitamin.

and are rich in vitamin A as well. Egg yolk is also considered a good source. The action of direct sunlight upon the skin is an important means of increasing the vitamin D content of the body. When vitamin D is furnished in optimum amounts, it helps to prevent fetal rickets, and facilitates the absorption of calcium and phosphorus. It is probably advisable for the pregnant woman to take cod liver oil, or its equivalent, throughout the period of pregnancy as a protection both to herself and her child. This is certainly true for the winter months when there is little natural ultraviolet radiation and the little vitamin D present in our natural foods may be further reduced. It is, probably, also wise to continue its use throughout the nursing period, but the amount transferred through breast milk to the baby is questionable and should be supplemented.

*Vitamin E.*—At the present time there is no clinical evidence that vitamin E is required by human beings. Experimentally with rats a diet deficient in vitamin E results in destruction of the germ cell in the male and failure of placental function in the female. This vitamin is widely distributed in food. It is found in wheat germs, seeds of plants, green leafy vegetables, muscle meat, and milk. Whether or not it is required in human nutrition, it seems probable that with this wide distribution of vitamin E the danger of shortage is slight.

**Practical Aspects of Dietary Instruction.**—From the foregoing discussion it is seen that while the total energy requirements during pregnancy and lactation are somewhat increased, there are strikingly disproportionate increases in the demands for protein, minerals, and vitamins. Failure to meet these changes often results in minor "subclinical" disturbances in health and not infrequently in serious consequences to mother and child. For these reasons clinical efforts should be made to see that these requirements are met.

Undoubtedly, a totally "naturally selected" diet would approach the optimum nutritional requirements of pregnancy and lactation. However, in considering the diets of civilized

people today, we cannot rely upon appetite as a guide in food selection as well as we could in primitive times, when all foods eaten were in their natural states. Indeed, the fact must be faced that modern diets are too often made up largely of milled, processed, and artificial foods. On the one hand, the consumption of milled and processed food has greatly increased. White flour and other milled cereal products from which most of the minerals and vitamins have been removed, form a large part of the diets of today. White sugar, the use of which has increased so tremendously in recent years has, also, in the refining process, lost valuable minerals still present to a large extent in molasses and brown sugar. On the other hand, while the same period has seen a marked increase in the consumption of fruits and vegetables, these are still consumed sparingly by a large proportion of the population, especially by families on low incomes. While the consumption of milk has increased, its daily per capita consumption is still very low in the light of our accepted standards of nutrition. The spending of a smaller proportion of the food budget for meat, white sugar and milled cereal products, and a greater proportion for milk, fruits, vegetables, eggs, and whole grain products, would do much to improve our nutrition. The dissemination of this knowledge through the instruction of pregnant and nursing mothers by the obstetrician, the pediatrician, the nutritionist, and by other workers in these fields, would do much to improve the health of our mothers, their children, and the family as a whole.

The nutritional demands of pregnancy and lactation, particularly the altered requirements for the several components of the diet, make clear the importance of careful instruction to pregnant and nursing mothers as to their daily food requirements. Indeed, no prenatal or postnatal care is adequate without such instruction. The patient should be questioned as to her customary daily food intake, her appetite, her food likes and dislikes, and her economic status. In the light of this information she may be shown those changes in her food habits which are both practical and advisable. When changes

## THE DAILY DIET DURING PREGNANCY AND LACTATION

*Milk:*

One quart daily is desirable throughout the period of pregnancy, and at least 1 quart during the nursing period.

Milk may be taken as a beverage with meals or between meals, or it may be cooked into the foods, as in cream soups, custards, creamed dishes, etc. Buttermilk may replace milk, and cheese may also be used in place of part of the milk.

*Vegetables:*

Two or more liberal servings daily of which at least one should be raw. (An ordinary serving equals 4 heaping tablespoonfuls [ $\frac{1}{2}$  measuring cup].) Leafy green vegetables, such as lettuce, spinach, cabbage, dandelion greens, chard, broccoli, etc., should be used daily. One potato is also desirable.

*Fruit:*

At least 2 servings daily. One of these should be a citrus fruit or tomato (raw or canned).

*Whole Grain Products:*

At least 2 servings daily of either whole grain bread or cereal. (One-half cup cereal = approximately 1 average slice bread.)

*Egg:*

One daily.

*Meat:*

One liberal serving of lean meat daily during pregnancy. Liver is valuable. Fish may occasionally be used instead of meat. Since a high-protein diet seems to favor milk production, meat, or its equivalent, may be used twice daily, during the nursing period.

*Butter:*

Should be used in moderate amounts.

*Cod Liver Oil:*

Or its equivalent, 2 teaspoonfuls daily. One of the accepted concentrates of fish liver oils in capsule form is acceptable.

*Additional Food:*

To meet daily energy requirements and food likes, remembering that much more food can be eaten during the nursing period than during the period of pregnancy without excessive weight gain. When there is a tendency to gain weight too rapidly, restrict foods rich in fats, sugars, or starches, such as gravies, bacon, mayonnaise, fat meats, macaroni, spaghetti, etc., rich desserts, as pies, pastries, cakes, too much ice cream, chocolate, candy, sweetened beverages, such as ginger ale, etc.

*Water:*

Six to 8 glasses daily unless there is need to restrict this amount during the latter part of pregnancy.

(It will, of course, be necessary, from time to time, to vary the above requirements to meet the individual needs of the patient.)

in food habits are advised the reasons for these changes should be explained in simple terms. Too much emphasis cannot be placed upon the fact that the difference between success and failure in obtaining the cooperation of the patient depends upon her intelligent appreciation of her dietary needs during pregnancy and lactation. This does not mean that she must have a detailed knowledge of food values, nor that she must sit down each day and check her diet for its quota of each one of the necessary components. A more practical method is for her to use a simple daily plan of feeding, expressed in certain foods or food groups, which will make certain that all the specific requirements are met. Such a plan as the one given on page 560 insures adequacy and yet permits much freedom in individual choice of food, while still teaching the patient the dietary essentials around which her daily menus should be planned.

It must be remembered that the consumption of the right amounts and kinds of foods is only a part of good nutrition. While the mother is learning good food habits she should be taught the value of proper rest, sleep, and exercise, all of which are so important to the establishment of good nutrition in its fullest sense.

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## CLINIC OF DR. JOE VINCENT MEIGS

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### THE SURGICAL MENOPAUSE

#### INTRODUCTION

In this discussion of the menopause all means of bringing it about artificially will be considered. Since the physiological menopause is due to primary ovarian failure, it is only by removal or destruction of the ovaries that it can be produced artificially. Diseases of the pituitary gland which may be responsible for a permanent amenorrhea and secondary ovarian failure are not included except where comparisons with this type of "menopause" are necessary. Debilitating disease and lack of ovarian development are also omitted. By the surgical menopause is meant a permanent amenorrhea accompanied by the signs and symptoms of the climacteric brought about artificially by three means only: radium, roentgen therapy and surgery.

#### RADIUM

That the radiologic destruction of the ovaries is permanent in some cases is not questioned, but in some instances, although amenorrhea may be present for a time, the ovary may merely be in a state of lowered activity and in time may become re-activated. This has already been shown in many instances by the return of the catamenia after radiation castration.

In young patients greater difficulty is found in bringing about a permanent cessation of menstruation than in older women nearer their climacteric or menopause. The use of radium to cause a cessation of abnormal bleeding in older

women is an excellent practice, at least so far as it can be judged at this time. That there is a distinct danger in the use of intra-uterine radium cannot be doubted, and the development of carcinoma of the endometrium in a recent patient treated eleven years before brings considerable thought to the problem of the later development of cancer in such individuals. The frequent occurrence of cancer on the site of a radium or roentgen ray burn must not be forgotten, and in any patient who has recurring bleeding following radium treatment the possibility must be considered. Young women are usually given very small doses of radium for the purpose of checking ovarian function without destroying it. Such doses usually vary from 200 to 600 millicurie hours. This dosage in all likelihood will not cause a permanent cessation of menstruation, and in from two months to two years the patient's catamenia will recommence. In older patients the dosage that is considered to be large enough to produce an artificial menopause is 600 to 2500 millicurie hours. In most instances the result is satisfactory; flowing ceases and menopause symptoms occur. However, even in some cases that have been given large doses menstruation has recurred and the menopause has not been permanently secured. It is in these cases that the possibility of malignant disease must be considered, for if the treatment is unsuccessful the presence of an overlooked tumor is a possibility; the chance of a granulosal cell tumor of the ovary is always present, and the definite possibility of a neoplasm starting in the radium reaction must be kept always in mind.

#### ROENTGEN RAY

Some surgeons, gynecologists, and radiologists prefer to use the roentgen ray as a means of establishing the menopause in patients who are bleeding or who have fibroids with abnormal catamenia, or in patients where the physician feels that the long drawn-out premenopause symptoms would cease by bringing about the true menopause.

In young women the roentgen ray is used in small doses to cause a cessation of abnormal flowing in the same way that

radium is used, but here again the chances are that a permanent cessation will not be brought about. Nevertheless, it has happened that in patients with low ovarian function (and it is in these that abnormal bleeding is often present) a permanent cessation of menstruation has occurred and the menopause has been created. This is sometimes very tragic, for the menopause is not a healthy state for the young because of the secondary changes that are brought about in the patient's genital tract. Avoidance of the menopause in youth should always be the rule. In older women with abnormal bleeding and with fibroids and other reasons for causing a cessation of flowing, roentgen ray therapy is very satisfactory. However, the practice of thus treating abnormal bleeding or fibroids without preliminary curettage and investigation of the endometrial cavity is to be deplored. This is a dangerous method, for large polyps, carcinoma, sarcoma, and other pathological conditions are often overlooked. It has been the author's misfortune to see a number of examples of this poorly conceived type of treatment; women who otherwise would have had a chance for life have been maltreated and all hope of cure has been taken from them. Cancer of the endocervix and body of the uterus often cannot be discovered by bimanual examination, and in these cases the employment of roentgen ray therapy without curettage to cause a cessation of bleeding and bring about the menopause is inexcusable. The amount of treatment given to produce the artificial menopause is well standardized by all roentgenologists, so that it is not necessary in this paper to go into the type and amount of treatment to be given.

#### SURGERY

The safest way of producing the menopause is the surgical method, for here the uterus and the ovaries can be removed, whereas in the radium and roentgen ray menopause they are left behind in a definitely damaged state. Ovarian pathology that might be overlooked in radiation treatment can easily be removed by surgical methods, and the patient cured. The removal of all ovarian tissue in young girls when the ovaries are

not pathologic is a great tragedy, and certainly they ought not to be removed unless diseased, in any woman under the age of forty-five. Most hysterectomies are done for abnormal bleeding or fibroids; it is not necessary in most instances to remove the ovaries in order to accomplish the purpose of the operation, and conservatism as regards this operation is highly advisable. If the ovaries are removed the uterus usually should be removed also, for the uterus without the ovaries acts almost like a foreign body. It is safer to get rid of this organ if it contains fibroids or polyps, for an organ that can grow one sort of neoplasm can also grow another of a more serious type. In older women when one is operating for fibroids, polyps, bleeding, or cancer it is wise to remove the ovaries, for they are already atrophied or abnormal and of no use in the body physiology, and the operation of hysterectomy is easier when the ovaries are removed than when they are conserved. Furthermore, such ovaries in cancer are often the seat of metastases, and it is sometimes impossible in gross to determine whether such a metastasis is present or not. In the case of women between forty and fifty, younger than the climacteric age, the question of removal of the ovaries is more difficult, but it is a safe rule to remove them if there is any evidence of pathology, and to leave them if they appear normal. The menopause should be avoided if possible because of its disagreeable symptoms and manifestations.

#### SYMPTOMATOLOGY

The menopause, as we have mentioned, is due to primary ovarian failure, and with such failure comes a chain of symptoms and of signs that are far from agreeable. The menopause is most frequently characterized as the time of hot flashes or flushes. This phenomenon may start in the face, or all over the body, or may begin in an extremity and rush to the face. There is a sense of suffocation and of great heat, and frequently the patient tries to get near an open window or door, or uses a fan. She is greatly concerned for fear her red face will expose her to the comments of her friends, but it is not

very frequent that this state is recognized, even by intimates. The flash, or flush, is similar to a blush, and it lasts a comparatively short time. This phenomenon is, however, a very frequent one, and often a patient may have from 1 to 30 per day. It is common for rest and sleep to be disturbed by periods of flushing that cause the patient to wake in a drenching perspiration. It is often necessary for the affected woman to change her nightgown two to four times a night. This may greatly disturb the night's rest and affects the performance of her daily duties. Hot flashes are but a part of her difficulty, however, and general nervous trends are well recognized; irritability is present and even serious nervous disorders can ensue, such as depressions, loneliness, lack of confidence, irritability, and even melancholia.

The physical characteristics also change in some instances, though not in all. It is not unusual to see the face become gross, the body heavy, and a certain amount of hair develop on the lip and chin. A moderate masculinization occurs in quite a few cases, but in some a more marked change toward the male type is seen. In others, however, femininity predominates; no one can fail to recall many old ladies of the most feminine types, yet these women have had a menopause for a number of years. Obesity also occurs, but may be due to a change in eating habits rather than to any change in the pituitary or other endocrine glands. Many old ladies are slender and fragile, and obesity and grossness are not always typical of the menopause.

Physiologically also there may be a change. A very feminine person may become dominant and commanding, and may assume definite male characteristics in her reactions to life. The libido may cease, but in some instances it shows a definite increase. Occasionally a woman may lose all interest in the opposite sex, only to be intrigued by her own. These, however, are the unusual and almost pathologic signs of the menopause. Certainly as we look about and see the numbers of older women well past the menopause who are living more contentedly than ever before we hesitate to classify the few

acquaintances who have signs of grossness and masculinity as normal older women. Some women who have suffered all their lives from dysmenorrhea, from the fear of childbirth, and from excessive flowing are completely made over by the climacteric, and look upon it as a relief from the dreads of younger years. These women bloom during the change, and live lives of great pleasure, having thoughts and ideas never before possible to them. Too much has been written about the ugly side of the menopause and too little about the great possibility of a more perfect and happier life. Just as before the menopause there are feminine and masculine women, retiring and aggressive women, weak and strong women, so after it the same contrasting types are found; the few instances of definitely pathologic changes are usually taken for the normal climacteric, so that a legend has been built up that terrifies all women who hear of it.

#### PATHOLOGY

In the radium or roentgen ray menopause certain changes take place in the ovaries that should be recorded here. These two organs atrophy, primordial follicles disappear, graafian follicles fail to form, and the entire ovary becomes fibrous. Even the interstitial cells and active stroma so evident in all ovarian tissue vanish, and all that is left is a tough, white, wrinkled ovary with an occasional cystic area surrounded by tough, hyalin-like connective tissue.

In the artificial menopause of any type the breasts atrophy, the epithelium that is usually stimulated by the ovarian hormones becomes inactive, and throughout the gland connective tissue is predominant. The breasts become smaller and firmer in the sense of being homogeneous and tough, and are often pendulous without the usual soft fulness. The uterus atrophies markedly and resembles the juvenile uterus, the length of the body approximating that of the cervix. There is but little muscular structure left, and the proportion of connective tissue is increased. The endometrium atrophies and in many instances but one layer of epithelium, either cuboidal or columnar, lines the cavity. Occasionally the endometrium retains a

structure, but the glands are often parallel to the musculature and not perpendicular as in the active sex life.

The cervix becomes more conical and pointed, and the external and internal ora are much diminished in size. Often the os may partially close, thus causing a pyometrium as the cervical cicatrix prohibits secretion from escaping. The epithelium is continuously desquamating, and eventually this cast-off tissue becomes softened and infected and a pyometrium develops. The vagina atrophies and the mucous membrane is often red and infected. This is due to the fact that the tissue of the vagina cannot resist moderate infection which adult tissue prior to the menopause would be able to resist. Frequently adhesions are formed owing to excoriated areas of mucous membrane sticking together. The possibility has long been considered that cicatrices of the vagina and cervix with the damming back of secretions are responsible for the development of carcinoma of the cervix or body of the uterus.

The vulva changes in appearance. It loses its softness and vascularity, becoming thinned out. The labia minora are obliterated, and sometimes even remnants of them are hard to find. It is in this stage of vulval atrophy that leukoplakic changes occur and the skin is thin and white, with the underlying tissues tough and close to the surface. Following the development of a true leukoplakic vulvitis, kraurosis or parchment-like whitening of the vulva takes place.

The urethra is frequently involved in the atrophy, and the tube contracts in such a way that normal voiding is impossible. As a consequence of this cystitis develops, and to clear up the frequency, urgency, and difficulty of emptying the bladder dilatation of the urethra is necessary.

The anus also shares in the marked atrophy and this may be responsible for very difficult constipation, which necessitates stretching or incision of the sphincter ani to bring about relief.

Except for the pituitary it is necessary to guess concerning the pathology of the other glands of internal secretions. The former gland apparently hypertrophies and oversecretes the gonadotropic hormone, prolactin A. It should follow that the

other glands overact on account of this hypertrophy, but it is well known that myxedema, or at least lowered rates of thyroid activity, follow upon the menopause rather than hyperthyroidism, which is not common. It is possible also that the adrenal may secrete less than formerly, although this is pure speculation. The hot flashes of the menopause may be due to an overstimulation of the adrenal with consequent hypersecretion of adrenals, and thus be partly responsible for the vasomotor phenomena. It is reasonable to assume that the masculinization seen in the menopause is due to oversecretion of the hormone of the adrenal cortex, which in neoplasms of that organ causes such severe changes to the masculine side. It is more likely, however, that after a temporary hypertrophy of the pituitary the gland secretes less and less of the thyrotropic and adrenotropic hormones.

Hypertension of the malignant type or of the milder type is often present at the time of the menopause but lack of estrin (theelin) or increase of prolan A has not yet been established as the real etiology. It is true that hypertension does occur at this time, but whether it is entirely due to failing ovarian function is not quite certain.

#### BIOLOGIC CONSIDERATIONS

In studying the menopause in the ovarian dysfunction clinic of the Massachusetts General Hospital, Albright has attempted to show in a series of papers what happens to the two hormones that can be assayed. There is an absence of estrin (theelin) in the true menopause, and there should be, for without the ovary no estrin is secreted. The prolan of the follicle-stimulating type of the anterior pituitary increases in amount. It is very probable that there is prolan present in every menstruating woman, but it is apparently not great enough to be found with the method of extraction employed in Albright's laboratory. It was noted in his experiments that the symptoms of the menopause do not follow directly upon the absence of estrin, for after surgical removal of the ovaries the estrin is at once negative, yet flashes do not occur for two



weeks to a month later. It was also noted that when estrin made its appearance in the urine following administration of the hormone as treatment the number of hot flashes did not diminish until the prolactin content was reduced or completely removed. It is also apparent that hot flashes fluctuate in numbers and that the fluctuation is in some way connected with the fluctuation of the amount of prolactin A in the urine and not related to estrin. For these reasons he suggests that prolactin A is in some way connected with the occurrence of hot flashes rather than lack of estrin.

Simple amenorrhea does not necessarily mean the menopause, for in various studies it was found that when no prolactin A and no estrin were present hot flashes were not a part of the picture. It is therefore evident that such a type of amenorrhea, which might be confused with the menopause, is due to a secondary ovarian failure, to a primary failure of the follicle-stimulating hormone (prolactin A) of the pituitary. Such patients may have a normal ovary capable of secreting estrin, but the pituitary, its governor, does not stimulate it to do so. One is able to differentiate the type of amenorrhea by a study of the twenty-four-hour specimen of urine and of the first morning specimen. When a given patient has no prolactin A and a normal estrin pattern she is considered in a normal state.

Chart 1 gives the various patterns of the three types of cases under discussion: the normal, the secondary ovarian or pituitary failure, and the primary ovarian failure.

CHART 1

	Prolactin A	Estrin
Normal	0	+
Pituitary failure	0	0
Ovarian failure	+	0

From the chart one should be able in most instances, after a careful assay of the urine, to determine the class into which a patient fits.

#### TREATMENT

In treating patients with the menopause it is necessary to do only two things: to bring estrin back into the urine, and

to reduce the amount of prolan A present. Some patients are very resistant to treatment and it is necessary to give large amounts of estrin to bring about the desired result. It is reasonable to assume that the estrin given by mouth acts as an inhibitor of the pituitary and thus less prolan A is manufactured, and if prolan A is in any way responsible for hot flashes its diminution should lessen their number.

It is better in treating patients suffering from nervousness, irritability and hot flashes to give estrin in effective amounts at the onset than to give small amounts and build up to an effective dose. This is so because such patients are skeptical of treatment, and if such treatment is a failure in the first week or two it is often difficult to persuade the patient to continue. Therefore, the method of treatment should be to give large doses at first and then cut down as necessary. That the treatment is expensive there can be no doubt, but once a proper dosage is established it can be cut down slowly to an amount the patient can afford. There is no doubt that given satisfactorily this treatment is eminently successful. Two injections of 50,000 international units per week should suffice, but an easier method of treatment is to give estrin by mouth. In the ovarian dysfunction clinic, progynon has been used with great success, and this has been carried on just as well in private practice. The method used by the author is to start a patient on two 600 rat unit tablets of progynon each day, and after a week, if no relief has been obtained, to raise it to 3, or to 4 or 5. After relief has been experienced the amount is cut down to 1 per day, 1 every other day, 1 every third day; then 200 rat unit tablets, 1 a day, 1 every other day, 1 every third day; and then to 45 rat unit tablets, 2 per day, 1 per day, and 1 every other day, or whatever dose will keep the patient comfortable. There is no doubt that nearly all hot flashes can be stopped, but to make a patient comfortable it may be necessary only to *reduce* them, and not to stop them entirely. The only measure for the proper dose is the comfort of the patient.

It is interesting that estrin given subcutaneously, by mouth.

or by means of vaginal suppositories relieves and improves the senile vaginitis experienced by menopause patients. Many of these women, complaining as they do of pruritus vulvae, are also relieved to a great extent by the use of estrin either subcutaneously, by mouth, or by suppository (more often by suppository than by either of the other two methods). The treatment can be followed by frequent vaginal smears, the presence of large squamous epithelial cells with nuclei, with or without pus cells, determining that a satisfactory change has taken place. This observation can be easily made in the office by removing a drop of discharge, placing a drop of water upon it, and examining it, unstained, under the high power of the microscope with the light cut partly down. Once the physician knows that the cells have changed, he will be able to assure the patient that her itch and discharge will presently clear. All cases of pruritus vulvae are not cured in this manner, but those due to vaginal discharge of the senile type are in many instances relieved of their symptoms.

Hormone treatment of the menopause is not the only method of helping these unfortunate patients. The use of carefully planned sedatives to assure them sleep at night, and thus enable them to handle their daily problems, is of great value. Sleeplessness coupled with nervousness, irritability, and so forth, is such a bad combination that if it can be broken up and the patient freed of at least some part of her symptoms, great relief can be expected.

The use of very strong iodine in the vagina with the patient anesthetized helps in great measure to cure the terrific senile vaginitis and disagreeable pruritus.

#### CONSERVATION OF THE OVARIES

In any discussion of the menopause, mention must be made of the fact that many surgeons and gynecologists think that the symptoms are no worse after the removal of both ovaries than after conservation of one or both of them. It has been my privilege to observe both schools of thought in this regard. Although no figures directly applicable to this argument are

available continued observation of both types of cases has led me to conserve one or both ovaries whenever possible when doing a hysterectomy on patients under the age of forty-five. It is felt by some that it is even more satisfactory to leave in a part of the endometrium so that a normal amount of menstruation may continue to occur, but this has not been my experience; the effect of such small bleeding is to cause constant worry and distress to the patient. In many instances it has been necessary to remove the retained cervix and its accompanying endometrium so as to put the patient mentally at rest. Figures that can be made to prove everything are available in the literature concerning hot flashes and ovarian conservation, so that it is an easy matter to advance any procedure and prove it as best for the patient. My own opinion is that in doing a hysterectomy in a young person up to forty-five years of age, conservation should always be practiced; that from the ages of forty-five to fifty it should be practiced if the ovaries appear normal to the individual operator; and that after fifty or after the menopause has occurred it makes no difference. Yet there are others who differ from this opinion and say that even in the atrophic state the ovary has a function, and that after removal of such ovaries patients show a definite lack of some factor that was important to them.

In an endeavor to determine how long the conserved ovary or ovaries of young people hold off the menopause, a study was made of 10 patients operated upon five years previously, the women at that time being less than forty years of age. Prolan A determinations were made four months apart on these patients five years or more after operation. Prolan A is rarely found in a normal individual, and if it were positive on two occasions this was taken as proof of at least the increased pituitary function that is found so commonly at the menopause. If this finding were also accompanied by a symptomatic menopause (hot flashes, etc.) then it could be concluded that the menopause had taken place. If, on the other hand, prolan A was negative—and it rarely is in a patient who has had the menopause—on two occasions four months

apart, and if the patient had no symptoms of the menopause, we might conclude that it has not been reached, in spite of the fact that the uterus, and in some cases one ovary, had been removed.

The results were quite striking. Three patients on both occasions had positive prolan A determinations and symptoms of the menopause, whereas 7 had two negative prolan A tests and no symptoms of the menopause. This small study is open to severe criticism on the ground that estrin determinations were not made, but it was so difficult to obtain twenty-four-hour urines for these determinations that it was decided that the presence or absence of prolan A and the presence or absence of symptoms of the menopause would have to suffice to allow deductions. There was no common factor in the series, either in age or total or supravaginal hysterectomy, but all the patients who had the menopause had only one ovary left in. On the other hand, only 3 of 8 cases with one ovary left in had developed the menopause.

It was therefore deduced from this study that the proper procedure in order to avoid menopause symptoms is to conserve as much ovarian tissue as possible and to protect the blood supply of the ovary carefully; this implies that the tube is not to be removed unless necessary, and that if it is removed it must be taken off at the tubal side of the mesosalpinx in order to preserve the back-and-forth anastomosis of blood vessels in the mesosalpinx. The ovary should be allowed to stay high in the pelvis, special effort being made to keep the infundibulopelvic ligament with the ovarian vessel in it loose and free from tension. The practice of tying the round ligament and the ovarian vessels together and attaching them to the top of the cervix or vagina is considered an unsatisfactory method of preserving a proper blood supply for the ovary.

#### CONCLUSIONS

- 1 The menopause is a phenomenon of primary ovarian failure
- 2 It has far-reaching physiologic, psychic, and physical effects

3. Its presenting symptoms are usually those of hot flashes and increased nervousness and tension.

4. It is probably connected with increased prolan A rather than decreased estrin.

5. Its relief is effected by means of sedatives plus treatment with estrin (theelin) either by mouth, subcutaneously, or by suppository.

6. Whenever possible the surgical menopause should be avoided in youth, and conservation of ovarian tissue ought always to be practiced.

7. Proper conservation means an anatomical consideration of the blood supply of the ovary. The tube should be removed as far away from the ovary as possible and there should be no tension on the infundibulopelvic ligament.

8. In at least 7 out of 10 patients operated before the age of forty conservation was successful in preventing menopause symptoms and prolan A was absent in two urine specimens five years later.

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## CLINIC OF DR. TRACY J. PUTNAM

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### THE DIAGNOSIS OF MULTIPLE SCLEROSIS AND THE OUTLOOK FOR TREATMENT\*

**Introduction.**—Multiple sclerosis is in many respects a peculiar disease. The symptomatology is protean and while there are several characteristic syndromes, a large proportion of cases fail to correspond to any of them, especially in the early stages. The "Charcot triad" may be so closely imitated by other diseases that a differentiation can only be made by autopsy. The *course* of the disease is irregular and unpredictable. The result of this diagnostic uncertainty is reflected in any attempts at a statistical study of etiology, prognosis and treatment.

The one secure starting point for any discussion of multiple sclerosis is its pathological anatomy. Nothing else can give us as clear an idea of what kind of a disease it really is. Fortunately, recent work has tended to simplify rather than to complicate the subject.

**Pathology in Relation to Symptomatology.**—The characteristic anatomical change in multiple sclerosis is the occurrence of numerous scars scattered throughout the central nervous system. Indeed, by the time death occurs it may be difficult to find any part of the brain or cord which is entirely normal (Hassin<sup>1</sup>). There are certain areas of predilection; the optic nerves, the periventricular region, and the pons are almost invariably affected. The scars are of various ages, and

\* This is the eleventh of a series of articles, based largely on investigative work financed by the Multiple Sclerosis Fund of Harvard University.

there is nothing unique about the process of healing, the rather complicated details of which need not concern us here. What is of clinical importance is, first that lesions showing every evidence of recent origin (edema, myelin in the early stages of breakdown, perivascular infiltration with glial cells) occur



Fig. 35.—Plaque from the cerebral white matter of an old case of multiple sclerosis. The center of the demyelinated area is composed of firm fibrous glial tissue. The edges contain myelin fragments in the process of breakdown, and an acute glial reaction with perivascular infiltration. Mason stain,  $\times 15$ .

in practically every case, about the edge of or adjacent to old fibrous scars (Fig. 35). Second, these fresher lesions go through a stage of acute edema before settling down to a relatively fixed state. And third, that extensive and obviously irreparable changes are found not only in the myelin but in the axis-cylinders of most plaques (Fig. 36). The extent of the



loss is indicated by a recent study of 35 plaques from 11 cases. Axis-cylinders were found practically absent in 18 of the lesions, and greatly reduced in 13.

The practical significance of these facts is obvious. First, because lesions are always multiple, the diagnosis is always

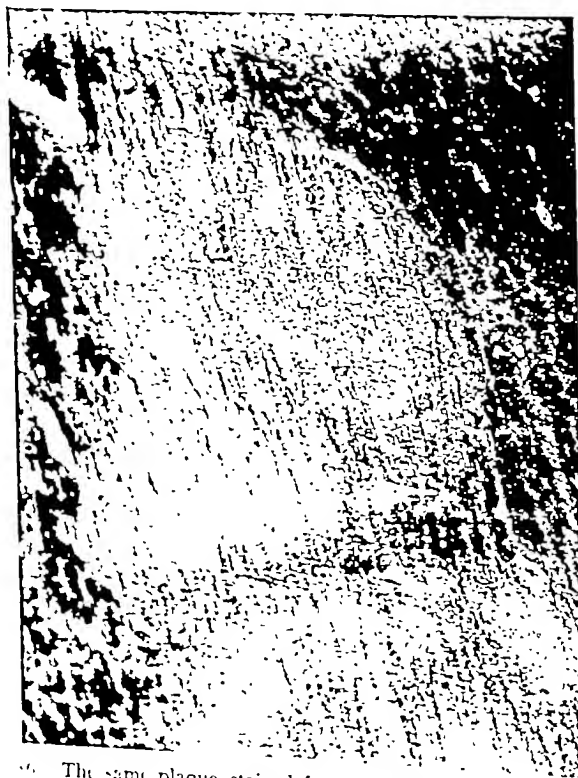


FIG. 56. The same plaque, stained for axis-cylinders. They are practically absent in the center of the lesion. Section from the same block as that shown in Fig. 55. Davenport stain,  $\times 15$ .

open to question unless symptoms or neurological examination discloses evidence of more than one lesion. Obviously, the symptoms may be extremely varied, and there is no predicting the rate or order in which they may occur. In general, however, there is a tendency to exacerbation or recurrence of already existing symptoms. Second, we should expect most symptoms to undergo spontaneous improvement of greater or

less degree, and again, the picture as a whole must be unusually characteristic to justify an absolute diagnosis if no remissions have occurred. Third, symptoms of long standing are usually permanent. More will be said below concerning pathology in its relationship to etiology, prognosis and treatment.

From a purely clinical point of view, perhaps the soundest way of giving a rapid survey of the possible manifestations of multiple sclerosis is to refer to the tabulation, which is taken

### TABULATION

TOTAL NUMBER OF CASES STUDIED 141 (MALE CASES 77, FEMALE 64)  
SYMPTOMS AND SIGNS ENUMERATED IN THE ORDER OF THE FREQUENCY OF THEIR OCCURRENCE\*

	Cases	Per cent
1. Abdominal wall reflexes were markedly diminished or absent in . . .	118	83.7
2. The chief complaint was weakness and stiffness of one or both lower extremities	115	81.7
3. Nystagmus was present in	99	70.0
It was chiefly horizontal.		
Horizontal and vertical in	17	12.0
Horizontal and rotary in	3	2.0
4. Babinski's sign was present bilaterally in	94	67.0
Unilaterally in . . . . .	16	11.3
5. Tremor was present in the extremities alone in	78	55.3
There was also tremor of the head in	31	22.0
6. Ataxia and adiadokokinesis were present in .	66	47.0
7. Deep reflexes in the lower extremities were increased in	126	90.0
Ankle clonus was present in . . .	61	43.0
Patellar clonus was present in	29	20.5
In 3 instances the knee jerks were diminished (tabetic type).		
8. There was a history of 1 or more remissions in	59	42.0
9. There were bladder symptoms in	57	40.0
Urgency was present in	18	12.6
Delay in starting urinary stream alone or in combination with urgency in 28 cases and incontinence in 21 cases.		
10. Speech was hesitant or otherwise disturbed in	51	36.0

\* From "General Symptomatology and Differential Diagnosis of Disseminated Sclerosis" by B. Sachs and E. Friedman. In: Multiple Sclerosis, Publication of the Association for Research in Nervous and Mental Disease, Paul B. Hoeber, Inc., Publishers.

# THE DIAGNOSIS OF MULTIPLE SCLEROSIS

581

	Cases	Per cent
11. The gait was spastic in .....	43	30.0
Spastic ataxic in .....	46	32.6
Ataxic alone in .....	15	10.6
12. There was evidence of facial weakness in .....	46	32.6
The other cranial nerves were very much less involved.		
The tongue deviated to the right in .....	14	10.0
There was difficulty in swallowing in .....	5	3.5
Uvula was drawn to one side in .....	4	2.8
The cochlear nerve was involved in .....	3	2.0
The vestibular nerve showed no response to stimulation in .....	2	1.4
Of the ocular muscles the internal rectus was involved in .....	6	4.3
There was ptosis in .....	2	1.4
The external rectus was involved in .....	3	2.8
13. Temporal atrophy was noted in .....	46	32.6
There was blurring of the disks or mild optic neuritis in .....	11	7.8
Vision was impaired without objective disk findings in .....	25	17.7
14. Pain, numbness and tingling were noted in .....	43	30.0
Objective disturbances in posterior column sensation were present in .....	24	17.0
Mild changes in pain, temperature and touch perception were noted in .....	23	16.3
(Among these were cases with hyperalgesic zones.)		
Astereognosis was noted in .....	5	3.5
15. There was a history of diplopia in .....	31	29.0
16. Cremasteric reflexes were diminished in .....	17	22.0
(Of the males cases.)		
17. Mental changes were noted in .....	22	15.8
They were largely those of mental infantilism and signs of neurosis or neurasthenia. One patient was in a state hospital with the diagnosis of dementia praecox. One patient showed the picture of Korsakoff's psychosis		
18. Emotional instability with explosive laughter occurred in .....	24	17.0
Defects of memory occurred in .....	7	5.0
19. Spinal tenderness was present in .....	17	12.0
It was chiefly midsacral.		
There was a history of trauma in .....	14	10.0
20. Papillary disturbances were noted rarely.		
Papillae were irregular in .....	6	4.3
They were slightly sluggish to light in .....	12	8.5
Atrophy was present in .....	16	11.3
21. There was a history of marked dizziness in .....	12	8.5
22. Incontinence of urine was noted in .....	6	4.3
No disturbances in rectal control were seen in any of our cases		

from Sachs and Friedman.<sup>2</sup> The signs and symptoms tabulated occur in almost every conceivable combination. Symptoms not given in Sachs and Friedman's table, but which have been observed in cases of multiple sclerosis in this clinic, include convulsions, paralysis agitans, trigeminal neuralgia and other "neuralgic" pains, muscular atrophies, and oscillopsia.<sup>3</sup> Mild leukocytosis and fever are common.<sup>4</sup> Stubborn constipation may be a most annoying symptom.

A characteristic phenomenon is the transient first symptom—often little noticed, and only recalled by effort on the patient's part. In a recent survey, Dr. Madelaine Brown found that 32 of 52 undoubted cases observed at this clinic gave a history of such a temporary manifestation at the onset. Numbness or weakness of one extremity or staggering were the commonest early symptoms, but diplopia and retrobulbar neuritis made up an important fraction of the group.

The age incidence of multiple sclerosis has been given by von Hoesslin<sup>5</sup> as follows: 1.4 per cent (of 516 cases) began before the age of ten years; 68.8 per cent between twenty and forty; 4 per cent after fifty. There have been reported instances of more than one case in a family, and I have seen two pairs of sisters so affected. The possibility of a mistake in diagnosis from the hereditary ataxias is, however, a real one (Mackay and Hall<sup>6</sup>).

**Precipitating Factors.**—The onset of multiple sclerosis, and the occurrence of exacerbations are not preceded by any unusual event in the majority of instances. The new symptom may develop so insidiously that it is impossible to date it, but about as often, the patient can say that it began at a certain hour. Occasionally, attacks are "apoplectiform." In a minority of cases, the disease begins or is grossly exacerbated by exogenous factors. Von Hoesslin found about 30 per cent of such cases among 516 records which he studied personally, and lists the factors as on page 583.

I have been greatly struck by the influence of pregnancy and menstruation on the course of the disease. One woman (in whom the diagnosis was confirmed by autopsy) began to

	Per cent
Injury and accident . . . . .	11.4
Pregnancy and labor . . . . .	5.8
Febrile diseases . . . . .	4.2
Overexertion . . . . .	3.9
Chilling . . . . .	2.3
Fright and emotion . . . . .	2.0
Poisoning . . . . .	0.5

have irregular menstrual periods toward the end of her course. Preceding each one she would have a two days' fever, and become completely paralyzed, often unconscious. Each of these events marked a step downward in the progress of her disease, which was practically stationary between them. I do not remember any female patient with multiple sclerosis who has gone through several pregnancies without an exacerbation.

**The Spinal Fluid.**—Examination of the spinal fluid is the only laboratory examination of great positive value in the diagnosis of multiple sclerosis. The following data, based upon 1068 cases, is borrowed from Merritt's article.<sup>7</sup> The cells were found to be increased (taking 5 as the upper limit of normal) in 28 per cent of cases. An abnormal amount of "globulin," as measured by qualitative tests such as the Pandy or Ross-Jones, was found in 45 per cent. Quantitative determination of protein revealed an increase above the normal in 24 per cent of the cases examined. Abnormal gold-sol curves were found in 71 per cent of fluids examined, a *first zone curve* being the type most frequently found. A slight increase of pressure is occasionally reported. In only 17 per cent of cases was the fluid entirely normal. On the whole, increase of cells or protein occurs slightly more often in cases showing progression than in those that are stationary.

Exacerbations occasionally appear to be precipitated by lumbar puncture, which should therefore only be performed when a real diagnostic indication exists. The effect is probably not to be ascribed to drainage of fluid, for I have seen similar reactions following venepuncture and other minor procedures. They are probably mediated by emotional disturbances.

It is the exception rather than the rule that the diagnosis of multiple sclerosis can be made positively on the basis of typical manifestations. More often it is made by the exclusion of such conditions as tumor of the brain stem or cord, neurosyphilis, syringomyelia, and combined system disease. An especial difficulty may be encountered in the diagnosis from the hereditary ataxias (Mackay and Hall<sup>6</sup>). In this group of diseases, the symptoms of multiple sclerosis may be imitated so closely as to deceive the very elect. The occurrence of other cases of organic nervous disease in the same family, the chronic course without remissions, and the absence of the characteristic spinal fluid picture are aids in diagnosis.

I shall make no attempt to set up criteria of differential diagnosis from disseminated encephalomyelitis, diffuse sclerosis, and neuroptic myelitis. It appears probable that these diseases represent variants of the same fundamental disease process, and transitional forms between the various groups occur.<sup>8</sup>

**Course and Prognosis.**—The usual current impression of multiple sclerosis is that it is a disease of relentless progression, bringing early and prolonged helplessness. Such cases do occur, and it is difficult to find a more tragic group in all of medicine. Of the 53 patients followed four years or longer by Dr. Brown, 11 are dead, 21 were helpless when last seen, or if dead, had been helpless for periods up to twelve years. It is common for a patient to survive three years after becoming bedridden, but rare for him to survive over six.

This is not the only possible outcome, however. Three of the patients who had at one time presented an unmistakable picture of multiple sclerosis, considered themselves perfectly well. Nineteen others were still ambulatory, and some of them at work. Remissions up to twenty years in length are recorded by von Hoesslin<sup>5</sup> and one of his patients survived the first symptom by fifty-one years.

The severity of the early symptoms appears to have little bearing on the ultimate prognosis. Thus, a patient who ten years ago was completely paralyzed in all extremities, with

various cranial nerve palsies so that he had to be tube fed. has since recovered except for a slight limp and is earning a living. On the other hand, sudden, fatal exacerbations may occur in the course of a chronic progressive case.

**The Problem of Etiology.**—All that has been said so far concerning multiple sclerosis is a matter of well-documented



FIG. 57.—Thrombus from the edge of a plaque in an old case of multiple sclerosis, in which death occurred during an exacerbation. Endothelial cells are invading an amorphous mass of platelets. A tangle of fibrin is seen in the right hand side of the lumen. Masson stain, oil immersion.

observation, to which few neurologists can take exception. When we come to the question of etiology, and thence to that of treatment, unanimity vanishes. A large number of divergent, often mutually exclusive guesses have been made in regard to the essential nature of multiple sclerosis. They have recently been well reviewed by Brain<sup>9</sup> and by Brickner.<sup>10</sup> It is to my mind a tedious waste of time to enumerate them again,

and to assemble the arguments which are held to support or confute them. I shall merely present an outline of the point of view which has gradually forced itself upon the workers in this laboratory who have occupied themselves with the subject for the past eight years; but before doing so, I feel I should warn my readers that these views are bitterly opposed by some authorities who have committed themselves to other opinions.

All of the data which have been collected by the group who have collaborated under the Multiple Sclerosis Fund has pointed to thrombosis of capillaries and venules as the origin of sclerotic plaques. Such thrombi (Fig. 37) have often been observed in various organs of the body in autopsies of patients dying from infectious diseases, certain forms of poisoning and without obvious cause. They have been produced experimentally by Kusama<sup>11</sup> and others by injections of homologous serum and other proteins, tissue extracts, suspensions of dead bacteria, bacterial filtrates, colloids, ether and metallic poisons. They occur frequently in allergic lesions. In cases of multiple sclerosis,<sup>12</sup> of some forms of encephalitis, and of carbon monoxide and nitrous oxide poisoning, they occur not only in the vicinity of the cerebral lesions but diffusely throughout the body.<sup>13</sup>

The relationship of the plaques to the thrombi is shown by the fact that all of the characteristics of the sclerotic plaque (including the so-called "inflammatory" phenomena) may be produced experimentally in animals by venular obstruction<sup>14</sup> and may also be observed in human pathology as a result of venous (more rarely arterial) obstruction of any origin.<sup>15</sup> Confirmatory evidence has been secured by the special methods of micro-incineration<sup>16</sup> and by a demonstration of abnormalities of vascular architecture.<sup>17</sup>

A comparison of the list of apparent precipitating factors given above will show that it corresponds closely with a list of factors accelerating the clotting of blood. Simon and Solomon have shown that there is a lability of coagulation time in many patients with multiple sclerosis.<sup>18</sup>



**Criteria of Treatment.**—If the hypothesis of the nature of multiple sclerosis just outlined can be accepted, it would seem *a priori* unlikely that any of the methods of treatment so far proposed should be particularly effective, and it has been my experience that none of them are. I have seen a large number of patients treated in this community and elsewhere with antiseptics such as the arsenicals and antimonials, forced spinal drainage, resection of the sympathetics, administration of autogenous vaccines, quinine, artificial fever, and vitamin therapy without being led to believe that any of the procedures have produced a change for the better in the course of the disease. Some of them clearly produced a change for the worse. To be sure, the proponents of each form of treatment report a certain proportion of successes, but the frequent occurrence of remissions makes their evaluation difficult. The tendency to euphoria and naïvety which so often accompanies the disease increases the difficulty.

Is it, then, hopeless to establish any criteria of the success of treatment? Certainly not. The accepted, obvious facts of pathology lay down certain limitations. As we have already seen, the formation of the lesion goes through two stages. The first is that of parenchymal damage or destruction, and there is every evidence that this is ordinarily a brief process. Then there is a stage of recovery of the less damaged tissue elements, and reparatory gliosis—a process extending over months or years.

*It is impossible to conceive that any treatment whatever can grow new axons in the central nervous system, and hard to imagine that the recovery of damaged axons can be accelerated (unless possibly by improving faulty nutrition). The success of a given treatment should be judged not on the basis of its effect on existing symptoms, but on its success in preventing relapses. I know of no treatment that does this.*

To be sure, the available statistics of the occurrence of remissions and relapses are wholly inadequate. To remedy this situation, Dr. Richard Brickner of New York has been instrumental in having a special commission appointed by the

American Neurological Association to study the subject, by reporting on groups of cases carefully observed, over a period of five years, under various forms of treatment.<sup>18</sup> A control series of 52 patients who have received no systematic treatment has been observed by Dr. Madelaine Brown at this clinic. While the investigation is still incomplete, and represents only a fragment of the study, some facts of interest may be gleaned from it. One is that in about 60 per cent of the cases, the initial symptom disappeared spontaneously. This comes very close to the proportion of favorable cases reported improved by practically any method of treatment (Brickner<sup>19</sup>), and it is all the more striking because the group contains many wholly unfavorable cases, in which the disease necessitated confinement to a hospital for chronic diseases or asylum almost from the onset. Three of these patients considered themselves well, and 12 were working. These figures also come close to the most favorable reports of the effects of treatment.

**What Help Can We Give to a Patient with Multiple Sclerosis?**—The fact that no satisfactory specific treatment for multiple sclerosis has yet been established does not mean that nothing can be done for patients suffering from the disease. At many points, the doctor's attitude and advice may make the difference between comfort and misery.

In the first place, the problem always comes up whether and when to announce the diagnosis to the patient. This is a matter of personal policy for every physician to decide in each individual case. My own point of view is that the situation must eventually be faced, and that it is usually better to have the depression which is often precipitated by the disclosure at a time when there is still hope that improvement may occur to mitigate it. The blow may be softened by pointing out that multiple sclerosis is by no means such an invariably hopeless disease as is sometimes stated, that more has been learned about the cause of the disease in the last decade than in all the rest of the century since it was first described, and that there is some reason for believing that an effective treatment may be found before many more years are over.

The real advantage of this candor lies in the fact that the patient may then often be saved the time, trouble, expense, and much greater aggregate disappointment which results from going from one enthusiastic therapist to another.

A careful survey of the patient's general health and hygiene should never be omitted. Of particular importance is a search for foci of infection, especially tonsils, teeth and sinuses. Anemia may be present, and should be corrected. The patient should have a diet which is on the meager side, and should avoid adiposity. Exercise within his strength is to be recommended. I have seen no advantage from prolonged rest in bed for patients able to be about. In female patients, pregnancy is to be avoided. It is my impression that most sufferers from multiple sclerosis do best in a warm, dry climate.

There are certain forms of *symptomatic* treatment which should be more widely known. Where spasticity is particularly annoying, small doses of bromides are often of striking benefit. Alcohol in moderate amounts may be useful, and does not seem to be particularly dangerous. The frequency and urgency of urination can often be alleviated by the use of sandalwood oil and atropine. An important point is that the urgency will often pass off if the patient makes up his mind to disregard it or distracts his attention with something else.\* Patients with hemiataxia may learn to avoid staggering by habitually leaning toward the more normal side. The disagreeable sensation of slapping the ground with the toes which is a common component of the spastic gait may often be mitigated by practice in placing the heel on the ground first, and rolling the weight along the outer edge of the foot to the toe. Foot drop may be avoided by orthopedic apparatus. Subarachnoid alcohol injection<sup>†</sup> may be tried for radicular pains.

In the treatment of spasticity, massage and electrical stimulation are to be avoided, as they merely increase the excessive muscle tonus. The foot placement exercises, so useful in tabes, are useless in cases in which the difficulty in walking is the

\* For this and the following suggestions I am indebted to my former associate, Dr. John B. McKeen.

result of intention tremor. Special "telescopic" spectacles are available for patients whose loss of vision from optic atrophy is relatively fixed and constitutes the most disabling symptom. When the bladder is completely paralyzed, an automatic tidal irrigation apparatus should be installed.<sup>21</sup> It also promises some benefit for cases of spastic, irritable bladder. Motorized wheel chairs may be of use to certain patients who are unable to walk.

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## CLINIC OF DR. E. GRANVILLE CRABTREE

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### THE TREATMENT OF URINARY TRACT INFECTIONS BY MEANS OTHER THAN THE KETOGENIC DIET

THERE is no perfect universal antiseptic for the treatment of urinary tract infections. Antisepsis alone is far too simple an approach to be adequate for cure in difficult cases. Even if it produces apparent cure recurrence often promptly takes place. For successful combat against stubborn infections other factors besides drug administration must be understood by the attendant physician if he is to be able to furnish that attention to detail which is an essential to success in the treatment of the infection and a safeguard to the patient. A perfect antiseptic for the urinary tract would be a menace to the patient if it permitted prompt removal of the signs of gross disease, which is often infection alone, without that condition having been recognized.

Considered numerically, it is probable that most infections which occur recover spontaneously. Treatment of this group gives abundant optimism for many forms of therapy. The relation of pH to recovery in these cases may be important. That relation is not yet proved. However, I have noted that in my surgical patients in whom urinary tract infection has been introduced in the course of surgery of the bladder or kidney, if prompt clearing of the infections takes place, the urine is almost always quite definitely acid, below pH 5.5, in reaction. Exceptions to this rule are noted.

At this stage in our knowledge of therapy it is sufficient to recognize three types of bacteria, about which we can accomplish considerable in treatment, namely, the colon bacillus

group, *Bacillus proteus* and the gram-positive cocci, staphylococcus and streptococcus. There are some definite differences in the method of attack for cure in the three groups mentioned.

As a preliminary to treatment, identification of the bacteria in the infected urine, and a sufficient number of determinations of the reaction of the urine to indicate the average  $pH$ , is important. Culture of the urine will often be misleading since, in mixed infections, the colon bacillus or *Bacillus proteus* may overgrow and mask the other slow-growing forms of bacteria present, such as staphylococcus. Gram's stain, when applied to the urinary sediment, will help to clear up the question of mixed infections. Culture is necessary, particularly in bacillary infections, to distinguish other forms of gram-negative bacilli, particularly *B. proteus*, from the colon bacillus group. Just how far mutations of bacteria influence treatment has not yet been determined. There is important progress to be made here, particularly in relation to virulence of the infection. At times it seems that in virulent infections acidification of the urine alone may give rise to symptoms in subacute cases. Certainly concentration of urine often gives temperature rises.

Where sugar is present recognition and proper handling is essential to successful treatment. Neither in my own experience nor in the literature, have I found sufficient data to enable me to make a statement as to the significance of high blood sugar readings or the presence of urinary sugar in acidification therapy. If nephritic conditions exist, closer observation of the urine during treatment by acidification therapy would naturally be given to detect signs of irritation early if they should occur. If renal damage is considerable the drug will not be excreted in sufficient concentration to be effective and storage will endanger the patient.

Even where the same bacterium, such as *Bacillus coli*, is the infecting agent, treatment is modified by four conditions in which an essentially normal urinary tract, as distinguished from gross pathologic changes, exists. These are acute febrile infections, subacute or chronic infections, infections in pregnancy and the puerperium, and urogenital infections. Need-



less to say, during acute febrile stages of infection, instrumentation, acidification of the urine, and concentration of urine are contraindicated. In the chronic form of infection one has the most favorable field for medication. In pregnancy there is a physiological dilatation of the pelves and ureters which is to some degree always present in pregnancy and which persists into the puerperium to a degree sufficient to modify treatment. Finally, in the male, pyelonephritis is so commonly complicated by prostatic infection, the symptoms of which are often overshadowed by the renal symptoms, that it is not recognized, receives no treatment and persists as the focus for chronic urinary tract infection with exacerbations. So minor a procedure as catheterization of postoperative retentions in the male with resultant minor degrees of cystitis may initiate such prostatitis which will remain unnoted, but eventually prove to underlie recurrent or persistent urinary infection.

A survey of the extensive studies made, over a considerable period of time, in the value of antiseptics in acute febrile pyelonephritis leads me to two very definite conclusions. The first is that it makes very little difference at this stage of the infection what the infecting organism is. The second is, that any form of active bactericidal therapy is unsound. The bacterium or bacteria concerned are in a virulent state, rapidly growing, producing fever, nausea, often severe vomiting, with attendant acidosis and shortage of fluid intake and excretion. The kidneys are edematous, subnormal in excretory ability and irritated to the point of albumin loss. This is no time for irritants such as hexamethylenamine with acidification, limitation of fluids as required in administration of some antiseptics, the use of heavy metals as in mercurochrome, or arsenicals. The addition of acidity to the acidosis already present especially in the face of diminished excretion, or the burdening of the system with dyes which will be excreted so poorly as to be present in the urine in sub-bacteriostatic or -bactericidal amounts, is equally without supporting logic. These patients have three major requirements. Rest in bed is essential. In home surroundings frequent trips to adjoining bathrooms are

to be discouraged. Even that amount of activity tends to prolong the disease. Vermooten<sup>1</sup> has called attention to the value of the elevated foot and lowered head of the bed with but one pillow as a means of shortening the course of pyelitis. Certainly the bed rest and the cramped sitting postures are to be condemned.

The second requirement is abundant fluid intake and excretion. Diminished excretory ability on the part of the kidneys in their inflamed condition, together with increased toxic products in the blood stream as a result of the febrile state, indicates the requirement for abnormal amounts of fluids to carry away even normal quantities of waste products to say nothing of the increased quantities which exist in the acute illness. If begun early in the disease this fluid can be taken by mouth up to 6000 cc. a day. Four thousand five hundred cc. will be the average requirement. If the patient is toxic when seen, to the point of nausea and vomiting, hypodermoclysis given slowly, preferably by multiple needles, will supply 4000 to 5000 cc. in twenty-four hours. This may either be normal saline or 2.5 per cent glucose. Saline is adequate without the glucose. Intravenous drip may be employed. It is less popular with me because failure to absorb from the tissues is a warning which intravenous fluid administration lacks. Seldom is more than one day of fluid administration by either method required before adequate fluid can be taken by mouth.

The third requirement is alkalization. High degrees of fever and prostration from acute urinary tract infection can be tolerated without acidosis, nausea and vomiting, if sufficient alkali is administered to produce a pH of 7 to 7.5. 45 grains of either sodium or potassium citrate or 60 grains of sodium bicarbonate is usually adequate to produce this result. More should be administered if necessary to produce the result aimed for.

The dangers attendant on instrumentation during acute febrile urinary tract infections are now well recognized. The exception is infection in pregnancy. This exception is made because of the pelvic residual urine which is characteristic of

this disease. Cystoscopic treatment here does far more good than harm. The possibility that an obstruction to drainage might exist, either in the upper or lower urinary channels, must not be lost sight of, but sought for, and promptly relieved where definite findings indicate its presence. Obstruction of ureters by pus plugs is a ghost which has not yet been completely laid. Partial obstructions, as from stones, can be temporized with safety in most instances until some abatement of acute symptoms has occurred.

It should be the purpose of treatment of acute febrile infections to shorten the duration of the acute symptoms as much as possible. Often mismanagement of the early stages of infections of the urinary tract is responsible for troublesome persistence through protracted fevers, starvation, anemias and debility which could have been avoided.

There is no contraindication to a liberal diet including proteins. Development of anemias is often extremely rapid. The alkalized patient need miss but few meals.

A patient emerging from acute urinary tract infections becomes safe for further urological investigation, local treatment or treatment by antiseptics, or for allowing out of bed after not less than four or five days of normal temperature and the loss of renal tenderness. Some patients require a longer delay. Previous to this time intravenous urography is apt to show the kidneys poorly, cystoscopy with retrograde pyelography to cause febrile reactions, and acidification of the urine especially when concentrated for therapeutic reasons to cause a return of fever. The type of antiseptics employed at this time will, in great measure, depend upon the organism found to be responsible for the infection. For the colon bacillus group of bacteria, acidification of the urine with ammonium chloride, sufficient to produce pH 5-5.4, and the administration of hexamethylenamine in 7½-grain doses, three times daily, is usually adequate and up to the introduction of the salts of mandelic acid, was the most efficient form of therapy. I do not see how it is possible to carry out treatment successfully along this line without pH determination. Simple apparatus is avail-

able for the purpose and should be used. Chlorphenol red test paper is of some help if kept in good condition until the time of use. The acidity of the urine is capable of great variation. Without pH determinations valuable time may be lost with the best of intentions toward the patient. Do not forget that old men have already, or acquire during fevers, residual urines. Women in bed are notoriously poor at emptying bladders without leaving residual urine and that both men and women have urethral strictures. Addition of bladder washes with nitrate of silver made up freshly from distilled water at three- to five-day intervals, will clear the bladder walls of adherent pus flakes and débris as well as have antiseptic value particularly in the above cases of small residual urines and the atonic postpartum bladder. A satisfactory silver nitrate solution, almost universally tolerated by the patient, can be made up quickly with 1-grain tablet of silver nitrate dissolved in 16 ounces of warm, distilled water. Do not throw an inflamed bladder into painful spasm with cold solution. Repeated fillings of the bladder are not well tolerated. A second filling will, of necessity, be at a lower capacity from the first if discomfort is to be avoided. Mercurochrome injections of 0.5 to 1 per cent solutions are used. Also argyrol in strength of 10 per cent, or other silver salts are used as an injection after lavage with boric acid solution. Silver is better. If cleansing only is desired, daily lavage with a bland solution such as boric acid solution 2 per cent, potassium permanganate 1:8000, and acriflavine, may be used.

Staphylococcus and streptococcus infections of the urinary tract are usually stubborn infections. Heathcote<sup>2</sup> has shown that the growth of staphylococcus was not definitely reduced at a pH of 5 by three hours' exposure to any concentration of formaldehyde in the urine that could be tolerated by the patient. Treatment by mandelic acid produces some cures. In one of my cases nineteen days of treatment at a pH between 4.7 and 4.9, failed to more than inhibit the growth. Often either acidification with ammonium chloride and hexamethylenamine or mandelic acid has cleared *Bacillus coli* from mixed infec-

tions and left the staphylococci or streptococci in pure culture. If the staphylococcus is still resistant to medication by salts of mandelic acid, alkalization of the urine should be done to a pH of 7-7.5 and acriflavine,  $\frac{1}{2}$  grain in enteric coated tablets, administered three times daily with the urine concentrated by an intake of 1500 to 1800 cc. Another medication, sometimes effective, is methylene blue in 2-grain chocolate-coated tablets administered three times a day. Greenberg<sup>7</sup> has pointed out that the gastro-intestinal symptoms sometimes encountered in methylene blue therapy, are due to zinc salt impurities. Unfortunately the purified dye has not been produced commercially. Where all else has failed neoparsphenamine given in 0.3-Gm. doses at five-day intervals for from 3 to 6 doses, is almost specific for the gram-positive cocci. It is reserved as a last resort because of the dangers attendant upon its administration in a condition by no means of the significance of syphilis. It must be given only after study of the patient and the attendant risk of administration and preferably by one expert in the treatment of syphilis.

Proteus infections will often yield to the salts of mandelic acid. In some of the apparent failures added lavage with silver nitrate has accomplished a cure. In those proteus infections in which acidification does not occur even with heavy doses of ammonium chloride, I know of little that can be done to combat this form of infection. Administration of mandelate or hexamethylamine then becomes wasteful. Fortunately, with all three forms of bacteria, the normal urinary tract is prone to rid itself spontaneously of infections in time. For this reason resorting to elaborate courses of antisepsis, or the more drastic forms of treatment, is hardly justified in the subacute stages of urinary infections.

Shifting from acidity to alkalinity with the avowed purpose of complicating the home conditions of bacteria in the urinary tract has an appealing and delightful simplicity suggestive of the practical joke, the purpose of which seems not often to be effectively grasped by the bacteria concerned. (Note the above remarks on spontaneous cures.) The effect of acidification of

the urine alone is bacteriostatic but not bactericidal in the lower pH ranges of 5.4 and under. No such bacteriostatic action has been recorded for alkalinity in experiments with any form of bacteria. There is no theoretical ground for expecting benefit other than the bacteriostatic effect of acidification when shifts from acidity to alkalinity are made. If acidification is attempted, as is commonly done, by the use of sodium acid phosphate, even that effect is not obtained since strong acidification cannot be produced by this drug.

After the elimination of those acute and subacute infections which either recover spontaneously or reach an early cure by the common forms of therapy, there is left a troublesome remnant of a few cases which are chronic infections. This group has been variously estimated as comprising from 5 to 10 per cent of the whole. They can be grouped into persistent infections or recurrent infections dependent on whether the urine becomes bacteria-free between exacerbations of symptoms. If the urine fails to clear at any time, gross pathology in the urinary tract, particularly conditions of urinary stasis, are probable. If complete clearing of the urinary tract from infections (as demonstrated by absence of bacteria, not pus cells) occurs, the likelihood of gross pathology is less but the probability of systemic causes is greater.

Chronic infections can best be approached for both diagnosis and treatment if the persistence of the infection is attributed to one of three major causes:

1. The condition of the patient,
2. Foci of infection,
3. Gross pathology,

and investigation conducted with the purpose of placing the patient in this classification.

I have already commented on the desirability of intelligent handling of the acute stages of infection that the patient may not emerge from them anemic and debilitated from a protracted illness, and suggested effective measures for the prevention of that condition. Unfortunately, urinary tract infections frequently occur as complications of surgery and debility from

other illnesses. They may then get dug in and reach the state of chronic infections before convalescence from the major illness takes place. Many Americans live in a constant state of exhaustion from overwork and overactivity in an attempt to enjoy *all* the possibilities of our modern life. There is also the faulty diet patient. One such with recurrent autumnal infection was found to have a dislike for summer foods and ate little, lost weight and acquired a yearly autumnal infection. Another patient reaches extremes of exhaustion in her social life. Her infections can almost always be predicted by watching the social columns in the newspapers. A mother, who was a confirmed Christmas shopper, with five children of school age who were all home with their friends at vacation time, had three recurrent infections in the five strenuous years of that activity all of which were in January or February of the new year. I find a higher percentage of recurrent infections in the upper classes with neither foci of infection, nor gross pathology encountered, than in the working classes. The working man has more gross pathology with his pus and bacteria. In addition some chronic infections are cured on adjusting metabolic problems.

Foci of infection seem to me to be the third in importance in these three groups. Teeth, tonsils and sinuses are occasionally incriminated yet it is surprising how often massive sepsis in these areas shows little relation to urinary tract infection either in its presence or after it has been cleared. It is most important in children. It must not be ignored. Bowel conditions play a very conspicuous part both in the incidence and the chronic stages of infection. A chronically overloaded bowel is perhaps most commonly found in these cases, and diverticulitis of the sigmoid is a very serious complication. The occasional case of perforation of such a condition into the bladder must not be overlooked.

In the male a symptomless prostatitis which is participating in a urogenital infection but receiving no treatment is perhaps the most common focus of infection. It may be responsible for a persistent infection with a constantly cloudy urine or for

recurrent infections which take place during exacerbations of prostatitis, which may be even a few years apart.

Gross pathology in the urinary tract either in the form of lower urinary obstruction with bladder residual urine, bladder malformations, diverticula, upper urinary, ureteral and pelvic obstructions all produce stagnant urine from which infection is eradicated with great difficulty by any known means short of correction of the defect. Stones and tumors are the other aids to retention of infections. The physiological changes in the kidneys and ureters due to pregnancy make these cases more nearly associated with this group although the obstructive factor is of necessity limited in duration to nine months. The chief danger is that if the degree of pathology is small the infection might be cured through the more effective measures now available in antisepsis and allow the condition to progress unnoted. Valuable time is often wasted in treatment to the detriment of the patient as in the case of a lady who received 156 pelvic lavages for infected hydronephrosis with stones, after many other antiseptic procedures had failed already. Infection may be the only indication of the presence of serious disease.

The commonly employed urinary antiseptics may be listed as follows: the dye group, the formalin-bearing drugs, the antiseptic acids, and the arsenicals.

**The Dye Drugs.**—Here are found methylene blue, acriflavine, pyridium and serenium, and mercurochrome. There are many others of less importance. All have other properties than the dye property.

Methylene blue, when administered in 2-grain chocolate-coated tablets three times daily in an alkaline urine with a pH above 7, has certain fields of usefulness. Thomas and Wang<sup>4</sup> found it of some value as an inhibitor and less value as a germicide against *Bacillus coli* and *Staphylococcus aureus* when the patient was limited to a fluid intake of 3 glasses of water daily. Hinman<sup>5</sup> found it more effective in staphylococcus and streptococcus infections than in the bacillary group when administered in alkaline urines with concentration. Greenberg used it successfully as a palliative in tuberculosis.



Acridine in doses of  $\frac{1}{2}$ -grain enteric coated tablets three to four times daily in concentrated alkaline urine showed bacteriostatic effects on both bacillary and coccal types of bacteria in half the cases (Walther<sup>6</sup>). Davis<sup>7</sup> had better success with 0.1 Gm. twice daily in concentrated alkaline urines infected with either staphylococci or *Bacillus coli*, producing cures in 13 out of 18 acute cases with 5 failures. In 27 chronic colon bacillus infections there were no cures. I have found it of most value in staphylococcus and streptococcus infections. There are better treatment agents for the gram-negative bacilli.

Pyridium and serenium have had in my hands no appreciable bactericidal or bacteriostatic effect on either the bacillary or the coccal forms of infection. Many other observers agree with this opinion. In a series of experiments in pyelitis in pregnancy the picture presented through the microscope of motile colon bacilli swimming sturdily along through a concentrated urine deeply stained with pyridium, went far to destroy my hopes of much help from these drugs. No other source of experience or information has revived my interest in them.

Mercurochrome, in spite of all that has been written, should be confined in its use to local applications to the pelvis or bladder.

Hexylresorcinol while not a dye drug is discussed here. It is administered in dosages of 0.3 to 0.6 Gm. three times a day and treatment is to be continued two weeks beyond the negative culture. The drug has not lived up to the promise with which it made its initial bow in 1924.

Methylene blue and acridine, even though both may produce gastro-intestinal symptoms, are the most effective drugs in this group. They are applicable to the coccal infections. Other forms of treatment are preferable by far for the bacillary infections. If gastro-intestinal symptoms occur the drug can be resumed after a short rest and tolerance for it seems to be acquired.

**Formalin-bearing Drugs.**—The second group to be considered is the formalin-bearing drugs. Hexamethylenamine is

the form in which this therapy is commonly and most effectively administered. Hexamethylenamine in acid urine has been the best therapeutic measure for treatment of the bacillary group of urinary tract infections previous to the introduction of mandelic acid. In properly acidified urine formalin is freed in antiseptic strength at the kidney level as well as in the bladder, namely, 0.005 to 0.007 per cent formaldehyde. In many instances it is adequate treatment for cure. It fails to cure some strains of *Bacillus coli*. Mitchell and Scott<sup>8</sup> found that certain strains of organisms were resistant to formaldehyde with marked correlation between test tube and clinical studies. If hexamethylenamine killed the organism in the urine, formalin killed it in the test tube. If it failed clinically it failed also in the test tube. The optimum  $pH$  for liberation of formaldehyde from hexamethylenamine in the urine is  $pH$  5–5.4. The common use of sodium acid phosphate with hexamethylenamine does not produce that degree of acidity from alkalinity. It is much preferable to use ammonium chloride to produce the acidity and to observe frequently to note if the proper acidity is maintained during treatment. Ammonium chloride should only be used in enteric coated tablets if gastric symptoms are to be minimized.

So important is acidification therapy both for the use of hexamethylenamine and mandelic acid that the theory and practice of acidification and alkalization should be taken up here.

*Acidification of the Urine.*—The true  $pH$  of normal urine depends in great measure on the phosphates by dissociation of  $NaH_2PO_4$  to  $Na_2HPO_4$  with liberation of an hydrogen ion. With complete dissociation of phosphate the  $pH$  lies commonly between 5 and 5.2. Increase in hydrogen ion concentration is accompanied by increase in ammonia excretion. Urinary volume seems to be inversely proportional to hydrogen ion concentration. Gamble<sup>9</sup> places the lower limits of normal acidity at about  $pH$  4.8 and doubts if acidity can be produced below  $pH$  4. He finds that the upper limit of alkalinity is  $pH$  8, even when large amounts of alkali are administered. Grey<sup>10</sup>

considers  $pH$  below 5, or above 7, pathological. The idea being that the bacterial infections have changed the normal  $pH$ , when figures below and above those readings are obtained. Marlow<sup>11</sup> found in his study of 141 normal young adults that the  $pH$  variation was from 5.1 to 6.8.

Administration of drugs by mouth as acidifiers is an attempt to produce as much free acid radical as is possible to be done. Regulatory factors convey an excess of acid over fixed base into the urine.

The commonly employed acidifiers are:

Sodium acid phosphate . . . . .	20 grains 4 times a day
Ammonium acid phosphate . . . . .	20 grains 4 times a day
Ammonium chloride . . . . .	15 grains 3 to 4 times a day
Ammonium nitrate . . . . .	15 grains 3 times a day
Ammonium benzoate . . . . .	40 grains daily

Sodium acid phosphate has been most widely used for urinary acidification but is the least effective of the group. Stockman and Johnson<sup>12</sup> find that it acts practically not at all in normally slightly acid urine. It produces slight acidity when the reaction of the urine is well on the alkaline side. The ammonium salts of hydrochloric acid, nitric acid and phosphoric acid are the best acidifiers. Their action is due to decomposition of the salt into ammonia and hydrochloric, nitric or phosphoric acid radicals. The ammonia is converted into urea and excreted by the kidneys. The acid is neutralized in the blood and tissues at the expense of the alkali reserve. Serious acidosis does not follow the administration of the usual doses of these drugs if the renal function is good. The same doses with moderate to severe renal impairment may produce marked deviation from the normal acid-base equilibrium with resultant changes in metabolic functions and the production of definite and severe symptoms of acidosis and even death.

It is probably best to select one acidifier and familiarize oneself with its use. Ammonium chloride is on the whole the most satisfactory.

*Alkalinization of the Urine* (Gamble<sup>9</sup>).—Where excesses of fixed base over acid is produced by the administration of al-

kalis there is need for an acid substance abundantly at hand which can be placed in the urine under control. Carbonic acid both suits these requirements and is available in practically unlimited quantities. Routinely it leaves the body base free by way of the lungs, but when needed can, to a regulated extent, be deflected into the urine. The concentration of free carbonic acid in the urine is of a stationary value of approximately the magnitude of that in blood plasma. As a consequence of this fixed value for carbonic acid, excess of base in the blood plasma is excreted as bicarbonate in the urine. Thus as the urinary  $pH$  rises above that of the blood plasma ( $pH$  7.4) the concentration of bicarbonate in the urine becomes greater. This concentration of bicarbonate which, in the presence of a fixed level for carbonic acid, would be necessary to force the  $pH$  of urine above 8 is terminated by the limit of total concentration of substances in urine. It has also been determined experimentally that ingestion of large amounts of alkali will not produce an alkalinity above  $pH$  8.

**Antiseptic Acid Therapy.**—Mandelic acid is a recent addition to our armamentarium for treatment of urinary tract infections. Its place is not yet definitely established. None will deny that for the colon bacillus group of invaders it is the most satisfactory agent yet produced. Many will question its universal application and success with the cocci and some of the less common organisms. The enthusiastic, almost fanatical rush to administer the drug at all times and often carelessly, as regards renal deficiency, acidity and toxicity of the patient in acute conditions has already made some doubt its efficacy. Its use is well established in the steep curve of acceptance with which we commonly greet an important novelty, then condemn and abandon it only later to take it up at somewhere near its true value.

Mandelic acid is a member of the benzoic acid group. It was selected for experimentation as an antiseptic because of all the acids tested it was found to be the most bacteriostatic *in vitro*. It has been known since 1883 that it would be excreted unchanged and not metabolized by passage through animals.

It is impotent except with strong acidity. In vitro at a pH 5.3, all bacterial life is killed at a concentration of 1 per cent. Mandelic acid cannot be administered as acid because of its irritating effect upon the stomach. Salts of mandelic acid must be used as the vehicle by which a proper concentration of the acid is made to reach the urine. As in the case of acidifiers of the urine the ammonium salt of mandelic acid is preferable because the ammonia radical will be excreted as urea leaving the acid free, thereby avoiding an unnecessary base. In an average normal patient, 12 Gm. of ammonium mandelate administered in twenty-four hours will produce a pH 5.3. Helmholtz and Osterberg<sup>13</sup> have demonstrated its diuretic action and cumulative rate of excretion at an established pH 5, with ammonium chloride. It is, therefore, an essentially short treatment course drug. These observers indicated a cumulative rate of excretion from 0.32 to 1.14 per cent in twelve hours during which 12 Gm. of mandelate were administered in 4 doses. They also showed that at a urine pH of 5 and concentration of mandelic acid to 0.25 per cent it was bactericidal for most organisms. The same results could be obtained at pH 5.3 with 0.5 per cent concentration or at 5.7 with 1 per cent concentration. These tests were made using sodium mandelate. They obtained approximately the same results by adding mandelic acid to normal urine of similar pH reading. There is no test for the acid in the urine. These determinations must be made through recovery of the acid from the urine.

Although mandelic acid may be considered as a foreign body in the circulation and in the urine, the need for adequate acidification to ensure its effectiveness introduces the question of acidification which is a chemical process within the body. The two drugs, the acidifier and the salt of mandelic acid, must, therefore, be considered together. Mandelic acid 3 Gm. with sodium bicarbonate 1.6 Gm., combined in solution to form sodium mandelate, is not neutral but has a pH 4.5. In consideration of the use of mandelic acid as an antiseptic one must take into consideration the combined acidifying power of the salt of mandelic acid and the acidifier. Helmholtz and Oster-

berg found that, by measurement of the urea clearance test, a dog suffered no permanent renal damage when 700 cc. of 1 per cent mandelic acid was injected intravenously over a seven-hour period. Presumably the dog had normal kidneys.

Acidification in nephritis, owing to diminished selective secretion by the damaged kidneys, at least justifies reasonable apprehension as to the safety of the procedure. Holling and Platt<sup>14</sup> report 2 cases of renal edema without apparent effect on the nephritis. Lyon and Dunlop<sup>15</sup> observed the CO<sub>2</sub> combining power which they checked before and after the treatment in a number of cases. They found it to be within normal limits except in one case in which 360 Gm. of ammonium chloride was administered in a futile attempt at acidification of the urine. The figure fell from 63 to 46 per cent (CO<sub>2</sub> combining power).

Untoward signs and symptoms may accompany treatment with mandelic acid. The use of acidifiers alone or in conjunction with salts of mandelic acid may produce red blood cells, casts, and albumin in the urine. Cubitt<sup>16</sup> found no ill effects from continued treatment when occasional casts and red cells appeared. Rosenheim<sup>17</sup> found one case with albuminuria showed increased amounts of albumin. In two of my own cases, the appearance of red blood cells was accompanied by bladder tenesmus where no bladder symptoms had been present before. Apparently after prompt cessation of medication all these signs quickly disappear.

The chief symptoms which may occur in the absence of renal insufficiency are buzzing in the ears, temporary deafness, nausea, vomiting, and dyspnea from acidosis. Minor symptoms are acid taste about the teeth particularly about fillings and general uneasiness when either from exercise or climate perspiration is profuse. In renal insufficiency symptoms may be extreme degrees of acidosis and even death.

Administration of the drug has been at the beginning through the use of sodium mandelate. Rosenheim's prescription for its use was 3 Gm. of mandelic acid and 1.6 Gm. sodium bicarbonate with flavoring of lemon and water sufficient to

make 1 fluidounce, put up in 16-ounce amounts. The administration was 1 ounce four times daily. If the acidity of the urine was not adequate, sufficient ammonium chloride was added. Since that time there have appeared other preparations. Ammonium mandelate combined with ammonium chloride in aromatic syrup has been marketed, under the trade name of syrup amdelate. Each fluidounce contains 12 Gm. of mandelic acid. The dose is 2 teaspoonfuls four times daily. Elixir of mandelic acid is also obtainable. It contains mandelic acid, 124 grains, instead of 185 grains, to the fluidounce, as compared with the syrup. Phosphomandelate is also on the market as a combination of ammonium phosphate and mandelic acid. The dosages are provided in separate envelopes with directions. As Cubitt has pointed out and my own experiences confirm, there is great variation in the amount of acidifier necessary to produce the desired pH 5.3 or less, at which mandelic acid acts best, both in different patients and in the same patient at different times. My preference would be for ammonium mandelate without ammonium chloride in syrup form. Sufficient acidifier could be added from day to day as the patient required.

After many and varied approaches, I have found that the most satisfactory method of administering the treatment was through preliminary acidification of the urine, by means of ammonium chloride until pH of 5-5.4 was obtained. This usually requires but from one to three days. Syrup of ammonium mandelate was then administered four times daily under daily observation of the urine. The ammonium chloride intake can be gradually diminished or often dropped altogether in twenty-four to forty-eight hours and the pH held up.\* Most of the cases of bacillary infections become bacteria free in that time. The mandelate is continued at a pH of 4.8-5.2 for a total of six to seven days after which a single dose daily of mandelate with 15 grains of ammonium chloride is administered for six to seven days longer, then the same dose on alternate days for a week more. Fluids are restricted to 1200 cc. for the first week then to 2000 cc. for the second week and fluids as de-

sired allowed during the third week. If recurrence of the infection should take place, treatment in regular dosages as in the first week will usually suffice to eliminate it, but often need not be carried beyond a day or two.  $pH$  readings of 5.5 or lower will often be noted for ten days to three weeks after medication has ceased.

The effectiveness of mandelic acid on both cystitis and pyelitis seems to me not yet to be clearly established. There is general agreement that it is eminently successful in the colon bacillus group of bacteria. Here it is at its best in the absence of any considerable degree of urinary stasis. That it will be successful with some degree of stasis is shown by the successful clearing of 9 out of 13 cases of pyelitis in pregnancy treated after the acute symptoms had subsided. Three of these cases are our own, the remainder collected cases. The proteus bacillus cases have been less constant. Presumably if sufficient acidification can be produced, cure may be effected. Where acidification does not occur it is useless. Both other observers and my own cases show instances where with mixed infections all bacteria are killed, both the bacillary and the coccal forms. In other instances the bacilli are eliminated leaving behind a pure flora of cocci. In one instance with a  $pH$  under 5 for nineteen days coccal infection remained unchanged under ammonium mandelate treatment.

There is no doubt but that complicated cases with gross pathology cannot be looked upon as suitable cases for mandelic acid therapy. It is, furthermore, to be hoped that no other antiseptic will ever be found which, by its use, might conceal to the careless observer pathology of much more significance than the infection which disclosed it.

In the male there are encountered many chronic bacillary urogenital infections. They are persistent over years. Many of these yield to mandelic acid therapy. Usually there are bacilli demonstrated in the renal and bladder urines and in the prostatic secretions. I have treated them in two ways, either by antiseptics first, then by massage, or by a course of massage given previous to antiseptics. In the former group



some persist as pyurias without bacteriuria for a considerable period of time and often recur. The second group is much more satisfactory. In this connection I should mention that several observers have noted that the semen is frequently found stained after oral administration of dye antiseptics. Disappearance of the colon bacillus from the vesicle and prostatic secretions in some of these cases under treatment with mandelic acid might indicate a similar drug distribution.

**Arsenicals.**—For the remnant of intractable coccal infections there is still one form of therapy which offers cure. That is the use of arsenicals. Neoarsphenamine, when administered in 0.3-Gm. doses at five-day intervals for a total of 3 to 6 treatments when required, will eradicate many of the stubborn coccal infections. Its administration is to be taken as seriously as when given for syphilis. There is less justification in producing complications by misuse of the drug when the nature of the infecting agent is of so much less significance than syphilis. Its use in coccal infections should be limited to the chronic type of infection.

Vaccine therapy need no longer be considered seriously in any except the very unusual case.

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## CLINIC OF DR. FRANCIS L. WEILLE

FROM THE ALLERGY CLINIC OF THE MASSACHUSETTS GENERAL  
HOSPITAL AND THE MASSACHUSETTS EYE AND EAR IN-  
FIRMARY

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### STUDIES IN ALLERGY: XXI. IONIZATION IN THE TREATMENT OF HAY FEVER AND VASOMOTOR RHINITIS

IN the treatment of ragweed hay fever by means of ioniza-  
tion, the following report is of interest.

Case I.—A thirty-six-year-old white male patient started having hay fever from the early part or middle of August to frost in 1928, following removal of a cyst from his right antrum. Skin tests by Dr. Francis Rackemann showed sensitization to ragweed and to elm but "inoculations never helped him; they made him worse." Violent sneezing starting with the ragweed season each year made him suffer severely. On August 6, 1935, he had an ionization treatment in a city in New York. He had "perfect relief" through the ragweed season.

On August 11, 1936, the patient came to the writer requesting similar treatment. He had no symptoms at the time. It was agreed that when he became severely ill the treatment would be carried out.

He had only slight symptoms from August 15 to September 6 when terrific sneezing, blocked nose, discomfort in the eyes, etc., started. He was seen for ionization treatment on September 8 while having violent symptoms.

The nasal mucous membrane was cocaineized with difficulty. The nose was packed for thirty minutes with 7 per cent cocaine muriate containing 0.5 per cent ephedrine hydrochloride. Except for slight garrulousness, no signs of a cocaine reaction were observed. Every point of the nasal cavity to be reached by the "ionode" (zinc, cadmium and tin) solution suggested by Warwick for the ionization treatment had to be anesthetized thoroughly both for comfort and in order to prevent expulsion of the packing by sneezing. Moreover the danger of slight displacement of the nasal electrode by sneezing was annoying.

The nose was completely but not tightly packed with cotton strips soaked dripping wet with "ionode" solution. The nasal electrode, described as being made largely of zinc, with small quantities of tin and cadmium was placed within this packing, but not in direct contact with either the medial or lateral

nasal wall. Before testing for the resistance in ohms in the circuit, further solution was added to the packing to soak it completely. It was desirable, but not possible in this case, to have both sides of the nose packed at the same time, as ionization of the first side would assure a low ohmage on the second side.

When ready for connecting the nasal electrode to the machine, the patient was allowed to lie down. The Burdick ionization machine was utilized; while this apparatus is expensive, it is said to be as "fool-proof" as possible. Numerous authors<sup>1, 2, 3, 4</sup> have described this instrument and the technic for using it. A most important point is having a resistance as low as possible, 1500 to 3000 ohms being indicated as desirable. In the present case a reading of about 6000 ohms was obtained. Rather than adjust the packing further, a minute amount of current—about 1 milliamperere—was allowed to flow through the circuit, the arm electrode having been made thoroughly wet and having been applied to the forearm. After about one minute, an ohmage of 4000 was obtained, then 2 milliamperes for two minutes were utilized and 5 milliamperes for one minute brought the resistance down to 3000 ohms. Following this a dosage of 10 milliamperes for ten minutes was given (100 milliamperere minutes). A similar procedure was carried out, but with greater ease, on the other side of the nose.

The lying position was a great comfort to the patient while he was having the treatment.

Upon removing the nasal packing, the mucous membrane had a grayish coating followed in a few minutes by the presence of gelatinous mucus, and later fibrinous exudate. The nasal breathing space was then completely obliterated.

When the patient had his former treatment in New York, fingercot packs had been left in the nose for forty-eight hours, having as their purpose the prevention of adhesions. As the writer has never found by experience that any such adhesions are produced, the patient was told that no such packs would be required. He had found them quite unpleasant, and was agreeably surprised. He was urged to drink fluids freely before his nose blocked completely and thereafter to do as well as possible. Symptomatic drugs, including codeine, were prescribed, especially to relieve headache. He was told to use an ice-cap and to keep his head elevated. He volunteered to keep a detailed report regarding his status following the treatment. It is quoted below without abbreviation.

Tuesday, September 8, 1936:

8.05—Left Dr. Weille's office.

8.10—On way home in the car, teeth in the upper jaw began to ache, particularly the molars.

8.25—Runny nose, both nostrils, watery discharge. Slight burning sensation inside the nostrils. Head clear—no trace of headache. Eyes clear—no tears or irritation in the tear-duct region. Slight impulse to sneeze when I answer questions.

8.30—Supper: appetite not so good. Can swallow water without much trouble—slight bubbly sensation in left nostril when I swallow. Right side completely blocked. No discharge. Left side running. Impulse to sneeze in right nostril easily suppressed.

8.35—Both nostrils blocked.

8.40—Molars no longer ache but front teeth do.

8.55—To bed. Took a glass of water and one of the larger pills.

9.00—Dull pain in front part of the nose. Teeth ache slightly. Temperature: normal.

After lying down experienced throbbing pain in nose. Pain is in rhythm with pulse.

During the next hour nose very uncomfortable. Nervous tendency to waggle lower jaw and grind molars. Breathe hesitatingly. Turn restlessly from one side to the other. Little cat-naps but find it difficult to go to sleep.

During the hour there were five wavelike and painful impulses to sneeze which could be stopped, however.

Some time after 10.30 went to sleep and slept without waking until my usual rising time at 6.30.

Wednesday, September 9, 1936:

6.30—Left side closed. Right side slightly open. (Was sleeping on left side when I woke.) No pain. Watery discharge dripping from left nostril. Eyes clear.

7.00—Breakfast. Little difficulty in swallowing.

8.00—Read morning paper. Right eye bothers a little and nose runs. Want very much to blow nose but refrain due to orders. Clear nose somewhat by gently massaging the front and sometimes clearing my throat. Discharge amber colored. Occasional impulse to sneeze suppressed.

8.15—Felt sleepy and slept again till 9.20.

9.20—Awoke but stayed in bed and dozed.

10.20—Got up and dressed.

Nose runs—watery discharge. Eyes don't bother me while I work. Slight and occasional twinges in right nostril. At such times right eye waters.

11.00—Eyes—especially right eye bloodshot.

Stuffed cotton in nose to prevent constant dripping and read book on Marketing.

11.05—Real twinge which made eyes water—right side of nose and right eye especially affected. Suppressed sneeze.

12.15—Left side a little open. Right side—heavy stuffed-up feeling, after I took out cotton.

12.30—Lunch. Good appetite and no difficulty in swallowing. During the meal the nasal passages cleared so that I could breathe freely.

1.00—Upstairs to nap. Fell asleep at once and slept soundly till 3.50. Breathing through nose—right side.

4.10—No particular sensation in nose with the exception of a slight roughed-up feeling.

4.50—Shaved—usually a delicate operation during hay fever time. No trouble

Breathe through nose but passages not entirely clear.

9.00—Bed and almost immediately to sleep.

Thursday, September 10, 1936:

8.00—Awoke but went to sleep again and slept until 8.00.

8.15—Breakfast.

Had to blow nose twice. Yellow discharge.

Eyes free from irritation. Left side of nose clear. Right side clogged and smarting occasionally.

Little or no trouble during the day.

7.30—Nasal passages obstructed by hardened discharge. Repeated blowing cleared nose but left membranes sensitive—especially the left side.

8.15—Sneezed once in back of throat. Other impulses to sneeze suppressed.

9.30—Bed. Slept until 6.30.

Friday, September 11, 1936.

6.30—Nasal passages filled with loose discharge. Blew nose gently and cleared it without difficulty. Left side wide open but sensitive to every breath. One spot especially felt raw and made my eyes water. Sneezed once.

7.00—Breakfast. Irritation calmed down but watery discharge persisted. Left nasal passage very clear. Right passage somewhat obstructed and sensitive.

Little trouble during the day.

Saturday, September 12, 1936:

6.30—Watery eyes and runny nose.

Clears after breakfast. Little trouble during the day.

Sunday, September 13, 1936:

6.30—Got breakfast and while being near the stove had quite an attack of sneezing, runny nose and watery eyes. Irritation persisted all morning but disappeared after dinner.

Monday, September 14, 1936:

6.30—Runny nose and watery eyes during the early morning. Persisted until 10 o'clock.

Sneezed three times but breathe through nose (both sides) without difficulty.

Following this report all symptoms disappeared.

October 26, 1936: the patient reported no hay fever whatsoever throughout the remainder of the ragweed season.

Because of the favorable effects of ionization treatment clinically upon many cases of hay fever it was decided to utilize this method in certain patients having vasomotor rhinitis. However, in the selection of cases preference was given to "difficult" problems. The following report is of interest.

**Case II.**—An eighteen-year-old white schoolboy had been troubled with nasal obstruction at all seasons as long as he could remember, with profuse watery nasal discharge and 1 to 3 sneezing fits daily. He was inclined to have superadded "colds" (apparently hay fever) in summer, with which he wheezed, but not severely. Straightening his septum, and removal of the tonsils and adenoids had not helped him. He was found to be sensitive to ragweed and timothy and to orris, house dust and kapok.

Examination of the nose showed a pale, boggy, granular nasal mucous membrane, with watery secretion in the middle meatus. The septum was still

somewhat deviated to the left, and its swollen mucous membrane made it appear thickened. The sinus x-rays were normal.

All manner of treatment, allergic or otherwise, failed to produce improvement and in March, 1935, Warwick ionization treatment of the nose was done. Complaints of watery discharge and sneezing then very largely disappeared, but the nasal obstruction remained very annoying despite definite thinning of the mucous membrane. The fact that there still remained a moderate high deviation of the septum to the left which had prevented the packing from being as effective on the left side as on the right, may have explained in part the greater mucous membrane thinning on the right side of the nose.

On June 28, 1935, the patient reported hay fever of a few days only with wheezing for about a week. Five days later he reported his nose as being excellent—no sneezing and one side of the nose constantly open.

The next year, in March, 1936, he was again advised to have ionization treatment. At this time the nasal mucous membrane was pale, but thin on the right side while very swollen on the left side. Warwick ionode packs were left in the nose for an hour, but no ionization was done. On July 28, 1936, he reported that he had been better for two weeks following this treatment, but after that his nose had been "terrible and as bad as it had ever been," chiefly because of nasal obstruction. Nasal discharge and sneezing no longer bothered him, nor did wheezing.

In an effort to increase the nasal breathing space, the anterior tips of the middle turbinates were removed. The pathological report was "considerable fibrous tissue for man of this age; epithelial surface denuded; in some portions of section there are questionable epithelial casts present in the gland ducts."

This case suggests that actual ionization is more effective than packing with the same solution, and that the treatment is more effective in relieving sneezing and nasal discharge than nasal obstruction in vasomotor rhinitis.

The effectiveness of both subepithelial diathermy cauterization and of ionization therapy is illustrated in the following report:

Case III.—A thirty-seven-year-old female patient had suffered from nasal obstruction, a dozen or more sneezing fits daily, watery nasal discharge, lacrimation and itchiness of the palate for many years. Her symptoms always continued throughout the year but were worse in the spring and fall. She had noticed that dust, tobacco, and face powder made her "terrible." A trip, away from the house where she had lived for ten years, to the mountains had been accompanied by improvement. A septum operation two years before had helped her for a few months. She had never had asthma.

Skin tests by the scratch method were negative; by the intradermal method an irritative skin was found. The nasal mucous membrane was very pale and extremely boggy. It responded poorly to strongly shrinking drugs. The sinuses were normal both clinically and on x-ray examination.

No real improvement resulted from various forms of medical treatment, so that subepithelial diathermy cauterization of the nasal mucous membrane was advised and carried out. Under local anesthesia diathermy coagulation of some of the stroma of each inferior turbinate was accomplished through a stab wound made with a long needle-like electrode. The resulting reaction in the nose lasted about two weeks. Following this treatment the patient was completely "cured" for five years. In May, 1936, her symptoms all returned. Her nasal mucous membrane appeared very pale and boggy. She became worse during the next few weeks, and in June, 1936, the nose was packed with Warwick ionode materials. The right side only was ionized. A gray deposit was observed on the mucous membrane of both sides when the packing was removed. Three days later, thick fibrinous membrane was observed in both sides of the nose. Microscopic examination of this membrane was reported: "Fibrinous exudate; no tissue recognized. Many eosinophiles are present."

In another week the nasal mucous membrane was found to be pink and thin and all symptoms had disappeared.

The patient was observed throughout the summer and fall; at the end of October she still remained symptom free.

One would suspect from this case that if both sides of the nose are packed, ionization occurs bilaterally when one side is ionized.

The value of subepithelial diathermy cauterization of the nasal mucous membrane is strikingly illustrated in this case. A prolonged follow-up will be necessary to determine the comparative effectiveness of the ionization therapy.

**Discussion.**—The most important point to consider in advising ionization therapy is the effect of the treatment upon the nasal mucous membrane. Two findings have been observed microscopically in biopsies from 4 cases after ionization: a fair amount of fibrosis of the stroma and metaplasia of the ciliated epithelium. The former presumably tends toward stabilization of an unstable mucous membrane. The latter places some doubt theoretically upon the desirability of using the method. However, from the practical point of view no adverse effects upon nasal physiology have been observed. Mosher<sup>5</sup> believes that such epithelial metaplasia may be disregarded as relatively unimportant in these cases.

Fibrosis of the stroma is seen after any type of nasal cauterization—from simple use of silver nitrate to subepithelial diathermy coagulation. Mosher<sup>5</sup> feels that ionization is merely



a refinement of such methods. There is the added advantage, however, that adhesions between surfaces never result from it, and that numberless sensitized surface cells are sloughed off.

So far as the effectiveness of the method clinically is concerned, it probably compares favorably with allergic desensitization treatment. It is likely to fail in cases having pathology other than mucous membrane instability which prevents adequate packing of the nose or which outweighs in importance the actual state of the mucous membrane.

**Conclusions.**—1. From patient's point of view the treatment may be exceedingly successful, as in Cases I and III, or rather disappointing as in Case II.

2. Actual ionization is clinically more successful than simple prolonged packing of the nose with the same solution, unless one side is packed and the other ionized at the same time.

3. The great theoretical drawback is that the treatment produces metaplasia of the epithelium. The fibrosis of the stroma which is induced is probably valuable in tending to stabilize the nasal mucous membrane.

4. The treatment itself is not particularly disagreeable to the patient.

5. The after-effects cause pronounced discomfort lasting for a day or two and gradually subsiding.

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### COMMONLY MISSED DIAGNOSES IN DERMATOLOGY

THE simple, everyday diseases of the skin are the ones which are frequently missed: psoriasis, scabies, seborrheic dermatitis, dermatitis venenata, epithelioma, etc. One may find, particularly in the state medical journals, many previous attempts on the part of practicing dermatologists to elucidate the commonly missed diagnoses of cutaneous medicine. In these papers, the list of diagnostic problems includes predominantly the usual skin disturbances with which most physicians are quite familiar, at least by name.

It seems that, in the practice of medicine, diseases of the skin appear much less often in classical form than they do in more or less atypical varieties, and the moment a skin disease becomes atypical, confusion arises. This confusion often disappears when the patient undresses completely and is carefully inspected from scalp to feet. Other areas of involvement are then found, often unknown to the patient, and some of these may possess diagnostic features which are lacking in the area representing the presenting complaint. The patient's denial of involvement of areas not open to ready inspection is often misleading, and his opinion regarding the status of his scalp or feet is always worthless. Collateral evidence of the greatest value is often found in these upper and lower poles of the body.

The specialist obtains a great advantage by the simple expedient of examining doubtful dermatoses with the binocular loupe. This advantage is available to anyone sufficiently zeal-

ous to make the purchase, and enlarges the readily available morphological data immensely.

Important evidence may be obtained in many cases by gentle curettage of lesions associated with dried exudates and secretions. An otherwise forbidding lesion may be reduced to great simplicity by removing well-guarded accumulations of detritus. Likewise, the true nature of more serious lesions may be revealed.

The time-honored dermatological custom of examining the patient before obtaining the history has justifications. An hour or more could easily be consumed in recording a detailed story from an introspective scabetic. Such a history would become immediately in large part worthless the moment the scabetic burrow was identified.

On the other hand, examination prior to history taking encourages snapshotism, and is apt to lead to undue subordination of the history. In the consideration of difficult diagnostic problems, a careful history is immensely valuable; its assistance is too often lost in a hastily executed survey of the case, and in overzealous confidence in the value of pure skin morphology as a sole diagnostic criterion. A vast amount of the common cutaneous ailments are either borderline or nondescript in character, and an opinion based purely on inspection has more the quality of guesswork than would be the case if properly reenforced by evidence pertaining to possible gross dietary aberrations, alcoholism, excessive nervous wear and tear, foci of infection, internal diseases under treatment by other physicians, sources of contagion, occupation, hobbies, etc.

A carefully analyzed story of the present illness is usually the most helpful part of the history, but, if this does not provide diagnostic clues, a surprising amount of valuable information can often be dug out of the other parts of a routine general history of the case. Such a history is vastly more important than a routine physical examination.

It is clear that bacterial and fungus infections, local irritants, internal toxins, and the various allergies may each produce more than one type of reaction in the skin. It is also

clear that a given morphological picture, such as the eczematoid, may be produced by several, if not many, various agents. Dermatology is thus full of pitfalls.

One of the most helpful aids to accurate clinical diagnosis in dermatology consists in making a list, either actually or mentally, of the possibilities which are suggested. One then takes up each alternative diagnosis in the differential, and attempts to exclude it or to prove its plausibility on the basis of details in morphology and distribution, as well as on the basis of other evidences from the general work-up of the case. An attempt is made to avoid snapshotism, and one avoids a precipitate answer to the patient's query as to what he has; a query frequently made the instant the doctor lays eyes on the eruption, and before he has had a chance to weigh all the evidence. Each lesion is carefully and separately examined, and the distribution is noted. As a case is inspected, going systematically from head to foot, various possibilities are suggested as each region is viewed. These suggestions are recorded, perhaps in writing, along with a list of all available data. It may then take hours or several days to correlate the data in hard problems. With practice, a clear answer emerges more and more easily from a mass of confused data.

This process of making a mental list of the possible diagnoses, and then of analyzing the list carefully is far superior to the usual approach of merely looking at an eruption and waiting for inspiration.

A list of the commonly missed diagnoses of the skin has been prepared. This list represents a collection based on personal experience, as well as on opinions collected from other papers dealing with this subject.

These diagnoses may be listed as follows:

Dermatitis venenata, including not only dermatoses due to vegetable poisons but those due to other chemical contacts. The general group of contact dermatoses and industrial dermatoses are thus included.

Epithelioma.

Psooriasis.

Seborrheic dermatitis.

Dermatitis factitia (self-inflicted lesions of the skin).

Pityriasis rosea (often confused with *tinea corporis* and secondary syphilis).

Erythema multiforme (often confused with urticaria and pemphigus).

Scabies.

Impetigo circinata (often confused with *tinea circinata*).

Bullous impetigo (often confused in the newborn with syphilis and pemphigus).

Herpes zoster.

Acne rosacea (often confused with *acne vulgaris*).

Dermatitis medicamentosa.

Lichen planus.

All forms of cutaneous syphilis.

Miscellaneous conditions such as coccidioidal granuloma, granuloma annulare, and lichen simplex chronicus.

Space does not permit a complete discussion of the differential diagnosis of all of these diseases of the skin. The list, itself, should prove serviceable as a guide to the practicing physician who would like to improve his diagnostic acumen. In the presentation of cases which follows, pertinent comments will be made in regard to important diagnostic criteria.

The selection of cases was made less in the hope of making it a comprehensively illustrative group than with the desire of presenting instructive as well as interesting cases. The main contribution of this paper lies in the case reports which purport to illustrate to the practicing physician a few points in the technic of diagnosing commonly missed skin diseases.

Case I.—G. M., a married woman of fifty-nine years, had been under observation for seven years with a dermatosis affecting the inner aspect of each thigh. Complete routine medical studies had been carried out several times. The skin and circulation of the lower extremities had received investigation in the hands of specialists. Almost every conceivable laboratory procedure had been carried out and no satisfactory interpretation or treatment for the dermatosis had been found. The patient was considering a pilgrimage to distant medical centers for further guidance, when the diagnosis was established by the simple procedure of examining the entire skin.

Inspection of the thighs themselves revealed on the lower inner aspect of each a large solid plaque of erythema, edema, and scaling with considerable lichenification and excoriation due to scratch. The true nature of the disease was completely disguised by the effects of scratch. It required considerable persuasion to induce the patient to remove her shoes and stockings to permit examination of her ankles and feet, and it was weeks before she would consent to a detailed examination of the scalp. A grade A dermatologist had been entirely satisfied with local examination of the thighs and had missed the diagnosis.

Inspection of the ankles revealed typical patches of psoriasis. There were well-circumscribed, raised plaques of erythema with characteristic layered, silvery psoriatic scales and bleeding points. There were similar patches in the scalp. It was then recognized that the plaques on her inner thighs were also psoriatic, bearing a very close resemblance to other areas as regards tint of erythema, elevation of the plaques, and sharp margination. The secondary changes due to scratch had resulted in such a degree of lichenification and excoriation as to disguise the nature of the disorder. This case was made elusive to a further extent due to the total absence of affection of the elbows and knees.

The diagnosis of psoriasis explained the resistance of the disease to treatment, particularly since treatment for psoriasis had never been carried out.

Case II.—W. B., an energetic young woman of superb general health, had been under treatment for two years by a grade A dermatologist, who had reported to the referring physician that the patient had "lichenification of the right elbow."

Examination of the right elbow revealed a typical psoriatic plaque with layered, silvery scales and bleeding points. At the time of the first examination, there were no such plaques to be seen anywhere except on the right elbow. During the subsequent year and a half of observation, typical psoriatic lesions appeared on the scalp, legs, thighs, and right knee.

The diagnosis was evidently overlooked in this case due to the fact that the first dermatologist who saw the patient was not curious enough to scrape the elbow. Had he done so, he would have recognized immediately the layered, silvery scales and the bleeding points of psoriasis. Observation of this patient over a period of eighteen months proved beyond all possibility of doubt that she had psoriasis.

Case III.—F. S., a married woman of twenty-seven years, consulted a grade A dermatologist for some blotchy lesions recurring on the face during the spring of each year. The dermatologist was satisfied with a simple inspection of the facial lesions, which he regarded as a neurogenous disturbance.

The lesions persisted as usual for two or three months and then vanished with the advent of early summer.

In the following year, the same lesions reappeared during the spring, and a second dermatological opinion was sought. Inspection revealed a papulopustular eruption, suggestive but not distinctive of psoriasis, until the lesions were carefully curetted. The typical layered, silvery scales and the bleeding

points of psoriasis were then demonstrated. Identical lesions were found in the scalp and on the back, but the elbows and knees were clear.

*Discussion.*—Many other missed cases of psoriasis could be added to the above.

It is inconceivable that a typical case of psoriasis would be missed by any well-trained physician. A high percentage of cases are, however, sufficiently atypical to become extremely elusive. It is a frequent occurrence for the elbows and knees to be spared, and this is very misleading. The patches themselves may not suggest psoriasis at all until scraped. The habit of scraping papulosquamous lesions will frequently reveal diagnostic layered, silvery scales and bleeding points in cases in which psoriasis is not at all suspected at first glance. Likewise, patches of erythema, not apparently scaly at all, may prove on curettage to possess even extreme layered psoriatic scaling. Also, the habit of careful examination of the scalp will often reveal classical patches of psoriasis, unknown to the patient, and these may arouse the suspicion necessary to recognize atypical psoriatic patches elsewhere.

There is no area of the body which may not be affected with psoriasis. The patterns of distribution are innumerable. Frequently, only one solitary patch is to be found. The mistake of examining only the area of skin presented voluntarily by the patient, as the chief complaint, is a common source of error.

*Case IV.*—M. H., a college student of twenty years, had eczema in childhood from the age of five to ten years, and had been having urticaria off and on most of her life. During recent years mild urticarial attacks had come about every six weeks. She had long known that she could write her name on her skin (dermatographism).

Seven months prior to dermatological consultation, while visiting in the Midwest, she began to notice severe generalized pruritus, marked exacerbation of her old urticaria, and occasional blisters on her fingers. There was definitely no suggestion of nocturnal exacerbation of itching.

Upon returning to the East, medical advice was sought, and her case was exhaustively studied. Complete general medical investigations were carried out. A thorough allergic study was done. Scratch tests showed definite reactions to timothy, orchard grass, and ragweed. Treatment by means of ephedrine, hydrochloric acid, and other measures was totally ineffective.



After seven months of study and treatment, the patient was referred for dermatological opinion. Examination disclosed on the upper back many excoriations and a number of faint macular lesions. On each side of the neck and upper chest, there were diffuse erythematous plaques with a moderate degree of lichenification and scaling. The scalp and feet were negative.

Between the thumb and index finger of the right hand there was an insignificant, dry crust evidently due to scratch, but it was interdigital and served to stir a very faint suspicion of scabies. On the right thumb there were two discrete, thin-walled vesicles. These vesicles definitely did not suggest scabies. There were no burrows, and there was nothing about the general distribution to suggest scabies. Except for the areas mentioned, the skin was completely devoid of changes.

Knowing that scabies is difficult to diagnose in persons of good hygienic habits, the vesicles were thoroughly fished, but no Acari were found.

Reexamination of the patient after a week of palliative treatment revealed on the right little finger a very small burrow. This burrow was fished and a typical *Acarus scabiei* was found.

The patient responded immediately and permanently to the twenty-four-hour treatment for scabies. At the last examination, seven months following treatment with two applications of Danish ointment, there was no return of itching and no evidence of scabies.

*Discussion.*—Scabies has been justly designated as at once the easiest and the most difficult diagnosis in dermatology.

In an exceedingly entertaining article concerning "Scabies Among the Well-to-do," Stokes<sup>1</sup> reports 53 cases of scabies from his private practice. The reader is referred to this article, the perusal of which is sure to improve his scabetic diagnostic acumen. Of these 53 cases, 37 had seen one or more physicians without relief; 8 had been seen by grade A dermatologists, and in 5 of these, diagnostic errors had been made. A total of 10 correct diagnoses had been made among 49 physicians who saw 37 of the patients.

Stokes lists as causes for the failure to diagnose scabies the following: (1) "a low index of suspicion"; (2) unfamiliarity with the typical scabetic burrow syndrome; (3) failure to see or recognize the burrow without the use of the lens; (4) failure to distinguish between scabies and the complications or sequelae, etc. The commonest erroneous diagnoses were: (1)

<sup>1</sup>Stokes, John H.: Scabies among the well-to-do: some principles illustrated by the case. Jour. Amer. Med. Assoc., Vol. 106, No. 9 (Feb. 29), 1936.

nerves; (2) hives (the scabetic urticarial reaction); (3) dermatitis (scratch plus pyogenic infection).

The diagnosis of scabies must rest chiefly on four observations (Stokes):

1. The burrow, especially on the hands and on the penis.
2. Nocturnal itching.
3. Distribution.
4. Identified contact.

**Case V.**—S. M., an engineer of forty-eight years, had been under treatment for two years for chronic ethmoid sinusitis. Ten months prior to dermatological consultation, he began to suffer from attacks of a dermatitis affecting the skin of the alae nasi, upper lip and adjacent portion of the left lower cheek, as well as the mucous membranes of the anterior portions of the nasal passages and the nasal septum. The eruption consisted of erythema, edema, scaling, crusting, and papulovesicular lesions.

The referring physician regarded the eruption as a dermatitis of bacterial origin, spreading from the sinuses. He thought that he cleared it up slowly by argyrol applications and lamp therapy. However, he could not prevent recurrences and sought dermatological assistance, not for diagnostic purposes but in the hope that x-ray therapy or some other special treatment would have more lasting effect.

The mystery of this case was solved by a carefully elicited story of the sequence of events involved in the present illness. A complete history in all other respects was entirely irrelevant.

**Present Illness.**—Twice per month for ten months the patient developed a frontal headache and a deep sense of stuffiness in the head. On each of these occasions, he employed a nasal spray. The headache and sense of stuffiness would then clear and a watery nasal discharge would set in. Exactly two days following each of these episodes, the skin eruption would appear. The use of cold cream, lenigallol, and other local preparations was ineffective in preventing the eruption.

The above story shows a close relationship between the induction of nasal discharge and the appearance of the eruption. One would naturally conclude that the discharge came from the sinuses and carried bacterial contaminants which invaded the nares and upper lip.

On the other hand, the nasal discharge was distinctly watery rather than purulent, and was more suggestive of hay fever than of sinus drainage. Subsequent studies proved that this discharge might well have been a sensitization reaction similar to that of vasomotor rhinitis or hay fever.

In the absence of knowledge pertaining to the exact nature of the nasal spray used, it was assumed that it might have been ephedrine. Accordingly, a standard preparation containing ephedrine in oil was obtained at the pharmacy, and was used in a patch test, carried out in a standard manner, using cellophane and a broad strip of adhesive tape.

When interpreted in forty-eight hours, this patch test with ephedrine was entirely negative.

Subsequently, the patient brought a bottle of the nasal spray which he had actually been using. A patch test performed with this material was violently positive. When the patient reported to have the test interpreted, he complained of intense itching at the site of the test. Removal of the adhesive revealed intense erythema and edema with innumerable tiny vesicles closely packed together.

Later it was determined that the patient had been using metaphedrine inhalant as a spray. Since his patch test was entirely negative to ephedrine, it was presumed that he was sensitive to the metaphen in his spray.

Treatment consisted simply in replacing the metaphedrine spray with an ordinary ephedrine spray. During the ensuing five months, he remained entirely free of his skin eruption. At the end of this time he developed a very mild, evanescent skin eruption of the upper lip. Except for this, the patient remained completely clear and was still having no trouble whatsoever at the time of his last written report ten months after avoidance of metaphedrine spray was advised. This ten months' record was in striking contrast to the preceding ten months, during which he had violent attacks of dermatitis twice per month.

It seems likely that his periodic watery nasal discharge was attributable to the effect of metaphen sensitization on the nasal mucous membranes.

**Case VI.**—H. W., an elderly retired business man, had consulted specialists in London and physicians on a transatlantic liner en route to the U. S. A. without obtaining any information regarding an extremely pruritic generalized eczematoid eruption.

Upon arrival in this country, his case was exhaustively studied by an internist. To both internist and dermatological consultant, the case was at first regarded as a considerably puzzling problem.

A second examination of the skin itself revealed certain peculiarities of distribution which solved the problem completely and paved the way for an extremely swift therapeutic result.

The morphological findings consisted of erythema, edema, scaling, fine papules and papulovesicular lesions, and numerous superficial ruptured vesicles.

The face, the hands, and the feet were entirely clear. The legs were involved only to a level just above the edge of the shoes, where the eruption ended abruptly at the lower border of some long woolen underwear which extended beneath the socks to just above the shoe level. The entire legs were involved from the knees to the ankles, but there was particularly intense affection beneath the garters which apparently increased the pressure and friction from the woolen underwear.

The thighs were less affected on the extensor surface than on the flexor surface, probably as a result of increased pressure and friction from the sitting position.

A sharply outlined band of dermatitis extended completely around the waistline. This area was coincident with contact with a woolen band which he had worn around the waist for some years.

The arms were clear but the forearms were markedly affected. A silk undergarment served to protect the arms, but below the elbows, there was contact with a woolen shirt.

The obvious deduction from the above facts was that this patient was suffering from a wool dermatitis. Upon reviewing the history, it was found that the patient had an attack of bronchitis in early September and because of this, began to wear the woolen garments mentioned. Shortly after this, his skin eruption began.

In treatment, all woolen garments were discarded and intimate contact between clothes and skin was limited to silk, linen, and cotton. Local treatment consisted of simple, soothing applications. All preparations containing lanolin were avoided because of the lanolin sensitization which, occasionally, accompanies wool sensitization. Because the patient was anxious to recover as rapidly as possible, calcium and hydrochloric acid were administered by mouth in the hope of expediting involution.

On the above plan of treatment, there was striking fading of the eruption in one week and almost complete clearing in two weeks.

During treatment, the flexor surfaces of the thighs relapsed and the dorsal surfaces of the hands became involved. Investigation revealed that as he was able to get around more, he began wearing a heavy woolen suit. He had not yet purchased long linen underwear to protect his legs and the chief area of contact with the woolen suit was brought about, in the sitting position, between trouser legs and flexor surfaces of thighs. The wearing of long linen underwear promptly cured this relapse.

Furthermore, it was noted that when sitting around in his woolen suit, he was in the habit of folding his hands and dropping them in his lap in a manner causing contact between the backs of his hands and his woolen trousers. Avoidance of this habit permitted rapid clearing of the hands.

One of the very interesting features of this case was the fact that the patient had been a wool merchant all of his life and, for many years, had worn, in the winter, garments identical with those to which he was obviously sensitive. In analyzing these cases, one usually searches for recent unaccustomed contacts and one tends to discredit the possible rôle of contacts which have been present without mishap for years.

The reason why this patient should have become suddenly wool sensitive after so many years of evident freedom from it, is food for thought. Careful analysis of all data in the case revealed nothing which was recognized as a clue in this regard.

Case VII.—L. S., a middle-aged business man, consulted his family physician because of an acute eruption of the hands and face. The dermatosis was regarded as very puzzling, and dermatological assistance was obtained.

Examination revealed an acute dermatitis made up of large amounts of

erythema and edema. Close inspection disclosed areas in which innumerable fine vesicles were closely crowded together as is often seen in poison ivy. Also, there were several lesions in which vesicles were seen to run distinctly in the lines of scratch.

The diagnosis of dermatitis venenata was made, and questioning soon revealed that for two weeks the patient had been caring for a primrose plant, pulling off leaves and breaking stems with his hands. The vegetable toxin was thus deposited upon his hands and was inevitably carried to the face.

*Discussion.*—There is probably no dermatological diagnosis more commonly missed than contact dermatitis. It is impossible to transmit by the written or spoken word that partially intuitive knowledge which enables the eye to suspect these cases. Having seen enough proved cases of dermatitis venenata in typical form, one acquires a distinctive mental picture of erythema, edema, and vesiculation. It helps to remember that on the face, the eyelids are apt to undergo rapid and extreme swelling. It also helps to know that the vesicles are likely to be small and exceedingly numerous, usually being closely packed together. It also pays to remember that bullae of varying sizes may be present among these small vesicles and that the vesicles may run in the lines of scratch.

A given contact dermatitis may, on the other hand, stir not the slightest suspicion of its true nature even to the eyes of the most experienced. In these cases, careful analysis and deductive reasoning will save the day.

**Case VIII.**—B. P., a widow of forty-seven, was considerably perturbed because of the sudden appearance of a circinate lesion on the chin. She sought the advice of her family physician who made a preliminary diagnosis of *tinea circinata*, but was not entirely sure of his opinion, and sought dermatological assistance.

Examination disclosed a circinate lesion made up of a very superficial "stuck-on" type of crust and the remains of a ruptured circinate bulla. There were no vesicles, no scaling, and no evidence that the lesion had developed as a consequence of the spread of a small lesion peripherally with central clearing; such as would take place in the development of a patch of *tinea circinata*.

The findings were typical of *impetigo circinata*.

**Case IX.**—M. M., a married woman of thirty-six years, was referred from a small outlying community. An appointment was made in the most urgent terms and the case was represented as an emergency. The patient and husband appeared in an utterly frenzied state of mind. For a week the most rigid

hygienic precautions had been observed for the prevention of spread, of what was definitely regarded as secondary syphilis, to the several children or to the husband.

Examination revealed an extensive papulosquamous eruption, which in general was quite consistent with secondary lues. Furthermore, there was total absence of itching, and there were constitutional symptoms consisting of pain in the back and knees. Because of this combination of symptoms, there was every justification for suspecting syphilis.

Inspection of the skin revealed on the left breast a large, oval, fawn-colored, markedly scaly lesion, strongly suggestive of the "mother spot" of pityriasis rosea. This lesion was much larger than any of the rest, and the patient volunteered the information that this spot had appeared about ten days or two weeks prior to the outbreak of the general eruption.

Elsewhere over the trunk, arms, thighs, and neck there were numerous oval, fawn-colored, scaly lesions, some showing a tendency toward central clearing and many running definitely in the lines of cleavage of the skin. There were no lesions below the knees, very few below the elbows, and none on the face.

Therefore, in all respects of morphology and distribution, the eruption was typical of pityriasis rosea. The total absence of itching was entirely consistent with pityriasis rosea. The confusing constitutional symptoms consisting of pain in the back and knee joints were found, upon more detailed analysis, to antedate by several months the onset of the skin eruption, and were, therefore, probably not related to it.

The laboratory studies consisted of dark-field examination and blood serological tests for lues.

One of the more prominent lesions was curetted until a slightly blood-tinged exudation of serum was elicited. The usual dark-field preparation was then made, and a diligent search for *Spirochaeta pallida* was carried out. The search was entirely negative.

To provide an immediate further basis for reassurance of patient and husband, a specimen of blood was tested by the Rapid Hinton method. This test was negative. The usual Wassermann, Hinton, and Kahn tests were done at the first visit, and these were repeated one week later. All six of these tests were negative.

Thus it was proved that the patient had pityriasis rosea rather than secondary lues.

One week following treatment with an erythema dose of ultraviolet light and local applications of 30 per cent aqueous solution of sodium thiosulphate, there was striking improvement of the eruption.

*Discussion.*—The mistake made in the above case was obviously a more healthy one than would have been the reverse. It would have been vastly worse to diagnose a case of secondary lues as pityriasis rosea and permit spread to others in the family. Furthermore, the case had puzzling features, and, in

accordance with the strict rules of this differentiation, the final opinion rested upon laboratory data.

In all supposed cases of pityriasis rosea, serological studies to exclude lues should be made routinely. An expert dermatologist is seldom wrong in his clinical appraisal of this differentiation. On the other hand, no physician can regard his clinical diagnostic acumen as great enough to ignore the routine of doing a Wassermann to prove the correctness of his diagnosis.

Case X.—C. J., a married man of forty-two years, consulted a general practitioner, promptly following the appearance of a penile lesion. The patient's emphatic denial of extramarital exposure when joined with a negative blood Hinton test apparently were very misleading to the general practitioner, who treated him for two weeks with local applications, thus depriving the patient of his golden opportunity for treatment in the seronegative primary state of syphilis.

When the patient failed to respond to dermatol and other local applications, he was referred for dermatological advice.

Inspection revealed on the glans penis two shallow ulcerative lesions with definite cartilaginous induration and extreme edema of the foreskin. There was marked bilateral inguinal adenopathy.

Because of the previous use of antiseptic local applications, it was impossible to demonstrate *Spirochaeta pallida* until after prolonged search of 8 separate preparations was made. Twenty-four hours later, after several normal saline soaks of the penis had been carried out, repeat dark-field examination revealed numerous typical *Spirochaetae pallidae*. A Rapid Hinton test was positive and routine Wassermann, Hinton, and Kahn tests were positive. Repeat Hinton and Kahn tests were positive, but the Wassermann was negative.

The diagnosis of primary syphilis was established on the basis of dark-field examination alone though it was supported by a Rapid Hinton test. Other serological evidence coming later was merely confirmatory, for antiluetic treatment had already been started. Had all serological tests been negative, the diagnosis would have been equally clearcut. The clinical evidence alone was almost incontrovertible. A positive dark-field was all that was needed for an absolute diagnosis and for prompt institution of treatment.

The diagnosis or exclusion of early syphilis must rest entirely on laboratory procedures. In the early primary stage, only the dark-field examination done strenuously by an expert can be relied upon because the serology is frequently negative.

As in the above case, denial of exposure, sterling personal characteristics, and negative serological tests for syphilis do not exclude syphilis.

Case XI.—W. B., a young unmarried man of twenty-one years, was referred for diagnosis.

Examination revealed a small, dry, pale, smooth, inconspicuous papule on the glans penis. There was no satellite adenopathy and nothing about the skin lesion itself to suggest its specific nature. Wassermann, Hinton and Kahn tests were all negative.

Dark-field examination revealed nothing in the first four preparations, but reexamination on the following day revealed numerous typical *Spirochaetae pallidae* in the first preparation studied.

Case XII.—Mrs. G. S., a middle-aged woman, had been under expert medical and dermatological supervision at frequent intervals for sixteen years. She was referred for dermatological advice regarding a number of trivial cutaneous complaints including a great many seborrheic keratoses and verrucae about the face.

A systematic examination of the face, ears, and scalp was carried out. Behind the right ear was discovered a medium-sized typical epithelioma, consisting of a hard, infiltrated plaque with a raised translucent border and a nodule in the upper margin. The center of the lesion was excoriated, but not ulcerated, and was occupied by a small blood clot.

A clinical diagnosis of epithelioma was made. The lesion was removed by surgical excision and showed on microscopic examination the typical histological features of basal-cell epithelioma.

Case XIII.—Miss R., a middle-aged spinster, had been under close medical observation for about one year. Several consultants were seen for various ailments but no one had paid much attention to a lesion on the right side of the nose. Finally she was referred rather casually for dermatological advice.

Examination disclosed a typical epithelioma located on the right side of the nose. The lesion measured 10 mm.  $\times$  7 mm. and was so distinctive that there could be not the slightest doubt regarding diagnosis. The border was raised and translucent, and the center was depressed. It was firmly indurated and moderate telangiectasia was present. There were several distinct nodules in the border.

Case XIV.—B., a retired business man of sixty-three years, was referred for treatment of a mild rosacea.

Examination revealed the usual findings of rosacea. In addition, on the right cheek there was a small typical epithelioma which had been overlooked. The lesion was entirely classical in its morphology and was made up of a raised, rolled, pearly, translucent border with a scaly, depressed center. Had there been more ulceration or more crusting, the epithelioma probably would not have been overlooked.

Case XV.—Mr. E. C., a graduate student of twenty-two years, had been under treatment for several weeks for what was regarded as a coated tongue due to reversed peristalsis.



Examination disclosed a tongue which was coated with a thick, whitish, furry material. This coating seemed to be made up of innumerable filiform projections, closely packed together. Material from this coating was easily removed by a curet. The underlying tissues of the tongue were erythematous. No other part of the oral cavity and no other part of the body was involved.

A dietary history revealed no evident abnormalities.

The clinical diagnosis was moniliasis of the tongue (thrush). Microscopic examination of scrapings from the tongue revealed budding yeastlike cells which upon cultural study proved to be *Monilia albicans*.

The patient was completely resistant to the usual forms of local therapy as well as potassium iodide by mouth.

His tongue cleared rapidly, completely, and permanently upon administration of liver extract by mouth.

**Case XVI.**—W. C., an artist of fifty-five years, developed, two weeks prior to examination, a nonitching eruption involving penis, forearms, and right axilla. Patient was seen by a diagnostician, who did not recognize the case as one of Lichen planus and referred the patient for a dermatological opinion.

Inspection revealed numerous small, flat-topped, angular papules. Some of these showed the typical glistening sheen and others the violaceous tint characteristic of Lichen planus. In the right axilla there was a distinct row of flat-topped angular papules, running as if in the line of scratch. On the inner aspect of each cheek there were milky-white streaks. All of the morphological criteria for the diagnosis of Lichen planus were therefore satisfied.

Routine Wassermann, Hinton, and Kahn tests were all negative.

**Case XVII.**—R. D., an unmarried secretary twenty-two years of age, had been under treatment off and on for four years for what was regarded by her physician as pemphigus. From time to time large bullae would appear on her legs, arms, thighs, and feet. These ruptured easily and were very slow to heal.

The patient was referred for consultation. Inspection revealed on her legs and feet one large and several medium-sized bullae. Around the margin of each bulla there was a definite erythematous halo, which served to distinguish it from the pemphigus type of bulla which arises from the apparently normal skin. In addition, there were several typical, circinate, urticarial lesions.

The combination of bullous lesions and urticarial lesions was considered to be diagnostic of erythema multiforme rather than pemphigus.

A complete series of scratch tests was negative.

Treatment by means of elimination diets, calcium, hydrochloric acid, ephedrine, etc., was ineffective.

A tenth injection of aolan was followed by a severe vagotonic reaction consisting of extreme erythema and edema of face, numerous generalized urticarial lesions, diarrhea, abdominal cramps, weakness, and a sharp fall in blood pressure. She recovered very satisfactorily from this reaction, following adrenalin injections.

Since the above episode, the patient has remained completely free of all evidences of erythema multiforme for eleven months.



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## SYMPOSIUM ON GASTRO-INTESTINAL DISEASES

The following clinics are included in this Symposium:

Andrew B. Rivers and Leslie A. Carlson: SOME EXTRAGASTRIC CAUSES OF DYSPEPSIA.

James F. Weir: PANCREATITIS.

Philip W. Brown: CONSTIPATION.

J. Arnold Bergen: THE TREATMENT OF DIARRHEA.

E. G. Wakefield: "SPASTIC COLITIS"; FUNCTIONAL DISORDER OF THE COLON AFFECTING YOUNG AND MIDDLE-AGED INDIVIDUALS.

Dwight L. Wilbur: VITAMIN DEFICIENCY DISEASES: THEIR DIAGNOSIS AND TREATMENT.



## SOME EXTRAGASTRIC CAUSES OF DYSPEPSIA

ANDREW B. RIVERS AND LESLIE A. CARLSON

---

A FRENCH writer referred to dyspepsia as the remorse of a guilty stomach. Although every physician knows that dyspepsia is not a disease in itself, it often remains the final diagnosis, and this frequently results in the dispensing of available measures which have been found to relieve belching, gas, or the various other symptoms that are included in the dyspeptic manifestations. Dyspeptic symptoms are usually the manifestation of nature's method of protesting against bodily abuses or are warnings of functional or pathologic disturbances of the gastro-intestinal tract. Nature does not confine her warnings to diseases of the stomach or even to organs utilized and concerned in the direct process of digestion. In this paper we are mainly concerned with the consideration of some of the more frequent and important extragastric diseases which manifest their presence by producing symptoms of dyspepsia. Almost any morbid process may herald its approach or announce its presence by causing some disturbance in the smooth, rhythmic process of digestion. Unfortunately, the degree or severity of the digestive disturbance is not necessarily an indication of the extent or gravity of the disease responsible for the symptoms. In order to appreciate this fact one need only consider the violent digestive disturbances experienced by neurotic individuals and compare these with the trivial disturbances of digestion caused by some extensive carcinomas of the stomach. Therefore, it is of the utmost importance to heed dyspeptic warnings as possible danger signals and to make every effort, especially in the presence of protracted and persistent disturbances, to ascertain the exact cause of any indigestion.

## SYMPTOMS OF DYSPEPSIA

Before proceeding into a more detailed consideration of the various causative factors of dyspepsia, it seems advisable to consider separately some of its more important symptoms.

**Pain.**—Pain is one of the most important and frequently one of the most baffling manifestations of disturbed digestion. This is readily understandable when one considers the mechanics of the production of pain in the gastro-intestinal and accessory tracts. In order to evaluate reasonably some of the painful phenomena experienced by dyspeptic patients, it seems advisable to review, at least briefly, the more important factors involved in the production of such pain. Painful impulses arising in the upper part of the gastro-intestinal tract may originate in the wall of the viscus, course along bundles in the sheath of the splanchnic nerves, cross over through the white rami communicantes of the thoracic nerves along the posterior roots of the spinal nerves, and thus may enter the posterior horn of the spinal cord. It is well to remember that painful impulses may also be conducted centrally through the sensitive cerebro-spinal somatic nerves, twigs of which supply the parietal peritoneum and many of the appendages of the posterior abdominal wall. The vagus nerves also contain some sensory fibers but it is doubtful whether these are very important in relaying painful impulses from the upper part of the gastro-intestinal tract to the brain. Lesions situated high in the gastro-intestinal tract, that is, about the cardia and esophagus, may send painful impulses to the brain through the phrenic pathways. Difficulty at once arises when an attempt is made to explain the genesis of pain from viscera which ordinarily seem practically insensible to the stimuli which produce pain on the surface of the body. All physicians have been present when extensive resections of upper abdominal viscera were performed under *local anesthesia* without serious complaint from the patient. An explanation of this paradox seems possible since it has been found that gastro-intestinal lesions can produce appreciable pain by way of fibers accompanying, if not part of, sympathetic nerves, providing an adequate stimulus has arisen in the viscus. This adequate stimulus is assumed to be an increase in pressure within gastro-intestinal segments, which results in stretching of the circulatory fibers of the viscus. It has been suggested

that in the stomach this spasm can be the result of hyperacidity which acts as a trigger mechanism that sets in motion spasm which in turn may constitute a stimulus entirely adequate to be appreciated as pain. Furthermore, muscular stretching could be incident to bombardment of peristaltic waves against an obstructing or partially obstructing segment anywhere in the bowel. This could be caused by organic obstruction, or by functional or sphincteric spasm of any circular muscle. There seems no doubt at the present time that spinal sensory nerves are of considerable importance in relaying impulses to the spinal cord, provided the lesion progresses beyond the confines of the intestines and invades neighboring tissues. Thus, as an example, the simple, clear-cut symptoms of uncomplicated peptic ulcer most likely would be visceral phenomena appreciated by means of afferent conducting mechanisms included within the sympathetic nervous system. With invasion of the tissues surrounding the intestines, warnings of the traumatizing effects of such invasion would be conducted through the nerves guarding these tissues, which would be branches of the spinal sensory nerves. In instances in which lesions are situated in the upper part of the stomach or in the esophagus, pain is not infrequently referred along the peripheral distribution of the phrenic nerve, thus producing pain in the neck or even in the tip of the left shoulder.

The diffuse epigastric distress that is almost universally associated with obstructing lesions of the gastro-intestinal tract, regardless of the position of such lesions, in all probability arises because of disturbed mechanics or disturbances in the wall of the viscus, which could be visceral phenomena that would be transmitted centrally along the sympathetic nerves.

In the progress of perforation to tissues surrounding a gastro-intestinal lesion, it would seem that the warnings of the traumatizing effects of such invasion would be conducted through nerves guarding these tissues, which would probably be branches of the somatic nerves.

Thus, it becomes intelligible how lesions even in distant regions, can indicate their presence by dyspepsia, since it is only necessary to produce disturbances in the mechanics of the stomach or upper part of the intestinal tract in order to produce an adequate stimulus such as spasm which may then be

interpreted as pain and relayed to the spinal cord along the fibers of the splanchnic nerves.

**Pyrosis or Acid Regurgitation.**—Pyrosis is a sensation of burning felt in the epigastrium or below the lower portion of the sternum. It is usually interpreted by the laity and by some physicians as evidence of excessive gastric acidity. Because of disturbed peristaltic activity the highly acid chyme is assumed to be regurgitated into the esophagus, the nasopharynx and the mouth, thus producing a sensation of heat in the epigastrium. This presumption is probably correct in many instances, although it is by no means always true. We have seen many instances in which patients regurgitated material which they described as sour and productive of a burning sensation, but chemical investigations of the gastric contents in these cases did not reveal any free hydrochloric acid. The reflux of acid chyme into the mouth is not necessarily indicative of hyperchlorhydria or of any disease, such as peptic ulcer, which is usually associated with increased peptic activity. Acid regurgitation occurs not infrequently in the presence of normal gastric acidity. These symptoms are not pathognomonic of any definite disease. Most frequently, in fact, they are the result of disturbances in peristaltic activity associated with errors in alimentation, or they are the result of functional diseases associated with reflex gastro-intestinal disturbances.

**Flatulence, Fullness, and Belching.**—Flatulence is a sensation of distention of the stomach and is usually felt under the sternum or throughout the epigastrium. This sensation, which is usually the result of an increase in intragastric pressure, is caused by an accentuation in the tonus of the gastric musculature. We have often been able to produce similar sensations involving the right upper abdominal quadrant or the hypogastrium by rapidly distending the duodenum or jejunum, respectively, with air or water. A similar type of distress very frequently results from an increase of intracolonic pressure or from hyperperistalsis associated with accentuated colonic irritability. The mechanism of distress in these instances is probably a splanchnic one, the adequate stimulus being produced by stretching of the circular muscle fibers within the gastrointestinal wall. In most instances, gastric flatulence is probably the result of swallowed air. Patients have noted that they

seem able to relieve their symptoms temporarily by belching: they have learned by past experience that if they are able to swallow air in sufficient amounts this will induce belching, which in turn will produce relief. Unfortunately, in many instances, the distention is not intragastric but rather to be found within the small bowel or the colon. Air-cribbing or aerophagia, therefore, results merely in an intensification of the distress. In many instances, flatulence, often associated with belching, is associated with functional disturbances. The loud, dramatic belching of the aerophagic, neurotic, dyspeptic patient is one of the oft experienced phenomena to which all physicians are exposed. Belching resulting from aerophagia is usually odorless, tasteless, or mingled with the flavor of the food which has recently been ingested. The belching occurring in chronic dyspepsias of an organic nature, particularly those associated with actual obstructive disturbances in the upper gastro-intestinal tract, usually has a bad odor. It may have the odor of hydrogen sulfide and is usually accompanied by other evidences of delayed emptying of the stomach or duodenum. Of the organic diseases associated with such symptoms, peptic ulcer and diseases of the gallbladder are the most important. It should be pointed out that the sensation of retrosternal fullness is not an infrequent accompaniment of coronary disease or cardiac decompensation. Esophageal disturbances incident to mechanical disturbances at the cardia also frequently manifest their presence by such symptoms.

**Anorexia.**—Appetite is assumed by many observers to be related to a sensation of gastric tonus. Ryle, in summarizing his views on the gastric sensations associated with appetite, suggested that these are in part a memory process and in part a local manifestation of efficient gastric tonus induced reflexly by the memory stimulus, by the more direct stimulus of seeing, smelling, tasting or swallowing food, or by some combination of these factors. He expressed the opinion that anorexia is a disturbance of motor function in which there is a diminished tonus or a pathologic rigidity of the gastric wall. He believed that prolonged fatigue is one of the more common causes of this symptom. He pointed out that profound emotion and prolonged worry may impair gastric tonus, probably through the medium of the sympathetic nervous system. During these cir-

cumstances there is often loss of sleep and physical rest, and thus fatigue at least may be a contributory factor. He suggested that in acute fevers and in chronic infections muscular tonus is impaired by the circulating toxins and he believed that the basis for anorexia was established in this manner. The loss of appetite associated with chronic alcoholism he attributed partly to the general effects of the poison on muscular function and metabolism and partly to the excessive secretion of mucus which inhibits normal stimulation of the gastric muscles and consequently the stimulation of appetite directly attributable to eating. It might well be assumed that in many other cases of chronic gastritis a similar etiologic relationship might obtain. The loss of appetite which is such a constant and pronounced symptom of carcinoma of the stomach is assumed to be the result of infiltration of the gastric wall by the growth. Ryle furthermore pointed out that in cases of leather-bottle stomach anorexia may be the only symptom and may occur independently of any extreme loss of weight, anemia, or any other factor such as pain or weakness. Anorexia, particularly that which affects elderly people and is unassociated with other systemic manifestations of disease, may indeed be a very important symptom and should invariably lead to thorough investigations of the upper part of the gastro-intestinal tract.

**Nausea and Vomiting.**—Nausea is characterized by a sinking or sick sensation in the epigastrium, usually accompanied, as Crohn has pointed out, by weakness, salivation, and dizziness. Crohn suggested that in the main nausea is probably a reflection of a state of irritation of the gastric mucosa, a sensory stimulation which is awakened in the afferent vagal fibers. He further suggested that the accompanying symptoms, such as dizziness, perspiration, and headache, are probably the result of a reflex general motor disturbance. Not infrequently, nausea may be produced among healthy individuals by disgusting odors, sights, and even by emotions. Ryle pointed out that oily and fatty foods and remedies which are known to inhibit gastric motility and secretion readily induce nausea, particularly among persons who have small appetites and hypotonic stomachs, and among those whose food requirements are low. Nausea is a common symptom in cases in which the value for the gastric acidity is low and the emptying time of the



stomach is prolonged. It is often found associated with chronic inflammatory conditions of the gastric mucosa. In many instances of functional disease, particularly in cases in which patients are of asthenic habitus, nausea is a frequent symptom which arises particularly when efforts are made to increase the amount of food that the patients should take. Nausea may result in vomiting, even in the absence of any unusual gastric residue or obstructive features. Many of the conditions which produce nausea may induce vomiting. The character of the material vomited is an important factor. If the vomitus includes only substances eaten several hours previously, the vomiting is no indication of the presence of an obstructing lesion. If, on the other hand, the material vomited includes substances eaten eight, ten, or more hours previously, the significance of the vomiting is very important. In order to ascertain whether or not the vomiting is an indication of obstruction, the use of barium or food motor meals should be advised. If there is definite evidence of residue when the stomach is aspirated nine hours after eating, this is a fair indication that actual obstruction exists.

#### CLASSIFICATION OF DYSPEPSIA

In their book, "The stomach and duodenum," Eusterman and Balfour classified dyspepsia, according to its etiology, as organic, reflex, systemic, and functional. This classification includes dyspepsia caused by organic diseases of the stomach and that caused by anatomic abnormalities involving the stomach. Inasmuch as this consideration will be limited to dyspepsia attributable to extragastric conditions it will be necessary to make some rearrangement of the classification of Eusterman and Balfour.

**Dyspepsia Attributable to Organic Disease of the Digestive Tube Contiguous to the Stomach.—***Esophagitis and Esophageal Ulcer.*—The most common disease of the esophagus is esophagitis. Vinson and Butt in a recent study reported the presence of esophagitis in 7.02 per cent of a series of 3,032 cases in which the patients came to necropsy. Definite symptoms occurred in 10.3 per cent of 213 cases in which a pathologic diagnosis of esophagitis was made. These authors expressed the opinion that vomiting is the important factor in

the etiology of this disease. They suggested that the anatomic structure of the esophagus makes it vulnerable to organisms of the oral cavity, and they were of the opinion that infections may occur through the lymphatic structures from the abdominal viscera. These authors also said that the most important symptom of esophagitis is a burning sensation over the lower part of the sternum. Pain and dysphagia also may occur and hematemesis occasionally develops. Clinically, it is difficult to distinguish esophagitis from esophageal ulcer which frequently occurs as an associated disease. An ulcer in the upper portion of the esophagus is usually traumatic. If the ulcer occurs near the cardia it may be peptic in origin. In approximately half the cases in which esophageal ulcer is situated at the cardia, the clinical history suggests the syndrome usually seen in peptic ulcer and the distress not infrequently is referred to the epigastrium. Dysphagia is a common symptom. A diagnosis of these conditions may be made by roentgenologic investigation, especially if an ulcer is present. Esophagoscopy usually will disclose the presence of inflammation or ulcerative disease involving the organ.

Carcinoma of the esophagus may manifest its presence by a distressing sensation of fullness or burning over the sternum. It frequently causes pain over the lower part of the sternum; the pain is definitely intensified during the act of deglutition. The diagnosis can usually be made by means of gastroscopic or roentgenologic investigation.

*Duodenal Ulcer.*—The organic disease which most frequently involves the tissues contiguous to the stomach and manifests its presence by dyspepsia is duodenal ulcer. One of the most characteristic features of the syndrome of duodenal ulcer is its periodicity. Attacks of variable duration alternate with periods of quiescence, which also are of variable duration. During the intervals between attacks, the ulcer may heal and at times may leave only a scar to indicate its situation. At times, an ulcer runs a fairly continuous course, without distinct periods of relief. Even in such instances, however, there are periods during which symptoms are mild. In the early stages of the syndrome of ulcer, the periods of distress are usually brief. Gradually, the period of quiescence becomes shorter. The attacks become more prolonged and frequently

more severe. The cause of the alternate periods of activity and quiescence is not entirely clear. Complications, such as hemorrhage or perforation, occasionally develop suddenly after a period of quiescence. Such complications at times develop during or following infections of different types. At times, heavy lifting, an alcoholic spree, or an unusually heavy meal may have preceded the occurrence of difficulties.

Reestablishment of the usual syndrome of chronic ulcer, with the characteristic pain, which is relieved by the ingestion of food or bicarbonate of soda, most frequently follows periods of prolonged unrelieved worry, unusual emotional disturbances, or catastrophe of any sort. Prolonged, intensive work associated with worry, or unusually fatiguing work, is blamed by many patients for their recurring difficulties.

The pain of uncomplicated gastroduodenal ulcer most frequently is situated fairly close to the median line and slightly above the umbilicus. The accurate localization of the pain is usually not possible.

Patients who have ulcer frequently notice that prior to the onset of their pain they experience a sensation of epigastric unrest, such as a slight rumbling or gurgling. This may stop, or in its place may come a sensation of hunger or occasionally a cramping sensation. These pains may be intermittent or they may be designated as a persistent cramp which does not become relaxed. The persistent pain, when very severe, is likely to be referred to the right or left upper quadrant of the abdomen, to the thorax, or to the back.

In cases of subacute or penetrating duodenal ulcer the pain is frequently referred to the right costal margin. The lesion then is probably definitely active, is progressing deeply into the wall of the duodenum, and is involving periduodenal tissues. With the development of referred pains in these cases, a change frequently occurs in other characteristics of the syndrome. The usual method of obtaining relief becomes less efficacious and periods of intermission become brief or entirely disappear. This deviation from the previous characteristics of the symptoms should suggest the probability of some change in the histopathologic structure of the lesion.

Although the pain caused by an uncomplicated peptic ulcer may be referred to the back, such a symptom, especially if the

tint to the scleræ. The value for the serum bilirubin ranged from 3 to 4 mg. per 100 c.c. The disease progressed rapidly. Within a few days the pain became more severe and opiates were required; nausea became increasingly distressing, the temperature became elevated and the rate of the pulse increased. Two days before death the patient vomited blood and passed tarry stools. Necropsy revealed a carcinoma involving the entire pancreas; there had been metastasis to the liver and two large ulcers had perforated into the duodenum.

Acute and chronic inflammatory lesions of the pancreas are extremely difficult to diagnose. The diagnosis of acute pancreatitis can rarely be made before operation. There may have been a history of previous attacks of pain in the upper part of the abdomen and vomiting which simulated gallstone colic, yet at operation or necropsy no evidence of disease of the gall-bladder or bile ducts may be found. The usual clinical picture consists of severe epigastric pain which appears suddenly and produces severe shock. The pain frequently is situated to the left of the median line. Muscular rigidity is absent but the pain is associated with tenderness and an indefinite resistance to deep palpation. Comfort has pointed out that the normal value for the activity of lipase, expressed in terms of twentieth normal solution of sodium hydroxide, is 1.5 c.c. for 1 c.c. of serum. In 95 per cent of cases of acute pancreatitis the values were considerably elevated.

Considerable confusion exists concerning the etiology and diagnosis of chronic pancreatitis. Pain is present in only about half of the cases, and when present it is hard to distinguish from that produced by peptic ulcer or cholecystitis. It may come on two or three hours after meals, is usually not severe, is frequently situated to the left of the midline, and may extend around the left side of the abdomen to the back or to the left shoulder. As a rule, administration of alkali does not produce complete relief. The passage of light, bulky, foamy stools which contain an excess of fat and muscle fibers is almost diagnostic. Glycosuria is present in a third to a half of the cases.

*Diseases of the Lower Part of the Small Bowel and the Colon.*—Diseases of the lower part of the small bowel and the colon usually are productive of some symptoms which suggest disturbances of digestion. Meckel's diverticulum, although

found in only about 2 per cent of all patients, contains heterotopic mucosa of the gastric type in about 20 per cent of instances. This may lead to the production of ulcerations, hemorrhage, or perforation. The indigestion which results may simulate the dyspepsia of peptic ulcer. At other times it may easily be confused with the signs and symptoms of appendicitis.

The following case illustrates the necessity of considering Meckel's diverticulum as the explanation for recurring attacks of indigestion.

A girl, aged eight years, had been subjected to an appendectomy because of abdominal pain and vomiting at the age of three years. Following this operation she had experienced frequent recurring attacks of abdominal distress. These attacks had become more frequent and she finally had passed tarry stools. Melena had been noticed on several occasions. Signs of partial intestinal obstruction had developed and laparotomy had been performed. At operation it had been found necessary to resect a portion of bowel because of intussusception. Before the patient had left the hospital she had had a recurrence of the abdominal distress. These attacks had continued and a diagnosis of "colitis" had been made. Treatment, which had been directed toward this condition, had brought about some relief and six weeks after the operation the patient had felt much improved. Two weeks before she came to the Clinic, however, she had noted tarry stools two to three times daily for four to five days. The passage of the stools had been followed by periumbilical pain. Operation revealed a Meckel's diverticulum with an ulcer at the base.

Vague and variable abdominal pains associated with tarry stools should always direct attention to the possibility of a Meckel's diverticulum, especially if the patient is a child.

Tumors of the small bowel and even tumors of the colon at times may cause physiologic alterations which are reflexly referred to the stomach. Early obstruction may be heralded by vague abdominal symptoms which may be considered as mild indigestion.

Regional ileitis, ileocecal tuberculosis, and colitis usually indicate their presence by varying degrees of indigestion. As a rule, questioning will elicit a history which suggests alterations in normal bowel habits and often reveals that the patient

has passed blood and mucus. In these instances the discomfort frequently is said to be referred chiefly to the umbilical region or to the lower part of the abdomen.

*Constipation.*—No discussion of extragastric causes of indigestion would be complete without adequate consideration of constipation. Patients who are constipated may complain bitterly of indigestion which might indicate serious "stomach trouble," and thorough roentgenologic and other examinations may be required to determine the true nature of the causative factor. These patients may complain of a sense of fullness, nausea, and vague abdominal pain. The pain usually is generalized, it occasionally is colicky in nature and frequently follows the course of the colon. Regulation of an obstinate constipation may cause a perturbing dyspepsia to disappear dramatically.

Hypersensitive patients, on the other hand, may appreciate normal physiologic processes more than does the average person. Many patients do not appreciate that the true criterion of constipation is the consistency of the stool rather than the frequency of bowel movements. Bowel habits vary among different people; some persons normally may have two bowel movements a day and others may have one movement every two or three days. Patients are frequently obsessed with the idea that they must have one or more bowel movements a day, and as a result they may fall into the enema or cathartic habit, which in itself may produce irritative symptoms.

The present-day habits of living no doubt are very important in the etiology of constipation. Concentrated foods, sweets, irregular meals which are eaten rapidly, nervous tension, lack of exercise, and inability to take the time to have a bowel movement no doubt are the most important causes. Many people ignore the call to stool and thereby dull the sensitivity of the nerve endings in the rectum. If this is repeated frequently, constipation may be the result. Dyspeptic symptoms, however, do not necessarily occur in such cases. As a rule, the next step is that the patients become concerned about this change of bowel habit and become "bowel conscious." They next resort to the use of laxatives and enemas as a time-saving method of having a bowel movement. They need only pick up daily newspapers or magazines to acquire plenty of free

advice on the dangers of constipation. They become thoroughly acquainted with the symptoms of auto-intoxication and become obsessed with the idea that they should have a bowel movement every day. They establish certain standards for this ideal stool and become "stool conscious." It is these patients who complain of a multitude of symptoms. They may complain of headache, dizziness, flushes, tiredness, insomnia, anorexia, vague abdominal symptoms, distention, and rumbling.

In such cases, sane habits of living, daily exercise, a balanced diet, and waiting for the normal physiologic evacuation of the colon may be all that is necessary to eliminate not only the symptoms but also the constipation. Unfortunately, once such patients have become acquainted with auto-intoxication and have established ideals for the perfect stool, they are never the same persons again.

*Hernia.*—Epigastric hernia is usually symptomless, but at times it may give rise to dyspeptic symptoms. There may be distress which occurs in the vicinity of the hernia. Catching of the mesentery or intra-abdominal viscera may cause twinges of pain. Flatulence may be an associated symptom. Inguinal hernia may give rise to nausea and vague abdominal pain or discomfort which most frequently is localized in the lower part of the abdomen. Unless careful physical examination is undertaken, the presence of herniation as a possible source of indigestion may be overlooked.

*Dyspepsias of Systemic Origin.*—In 15 to 20 per cent of all cases of dyspepsia the condition is reflex. One often forgets that the stomach may be the voice box of the neighboring abdominal organs; infrequently, it becomes the first organ to appreciate disease at a distance.

*Heart Disease.*—Disease of the heart deserves first mention if only to emphasize again the fact that the diagnosis of acute indigestion frequently gives way on further questioning to that of coronary thrombosis.

Heart disease not infrequently simulates an acute abdominal emergency. Patients frequently assume that symptoms are the result of indigestion when even a few cursory questions will make it clear that they have had an attack of angina pectoris. These patients may complain of pain which first appears, or increases in severity, after meals. Flatulence and fullness in

the epigastrium may be associated with the pain. These patients may not appreciate the effect exertion has on the production of the pain. It is not unusual for cardiologists to see patients who complain of diffuse pain in the thorax and upper part of the abdomen. This pain is associated with abdominal fullness and flatulence which are closely related to the taking of food and obviously are not related to exertion. It is difficult to convince these patients of the nature of their malady. The diagnosis in these cases is most frequently made from a painstaking history, with particular reference to the influence of exertion on the production of pain.

Myocardial failure, which is associated with congestion of gastric vessels, enlargement and congestion of the liver, and, at times, with ascites, may produce fullness, epigastric discomfort, belching, and anorexia, which are more distressing to the patient than is the shortness of breath.

In advanced cardiac failure the signs of the disease make the diagnosis clear. In the early stages of cardiac failure, however, before definite evidence of cardiac decompensation has become apparent, it may be difficult to make a diagnosis. If rest in bed or a restriction of physical activity results in disappearance of the symptoms, early heart failure should be suspected. This test is insufficient proof, however, to incriminate the heart because dyspepsia caused by other conditions may disappear after rest. Even though the heart is suspected, it is wise to wait for definite signs of cardiac failure before making a final diagnosis.

*Intrathoracic Disease.*—Intrathoracic diseases, such as basal pleurisy and tuberculosis, may produce symptoms referable to the abdomen. The extension of pain which originates in the pleura has led to many unnecessary operations for alleged cholecystitis or appendicitis. The acute pleural disease is usually recognized without much difficulty. This may not be true in cases of chronic or recurring pleural irritation. There are many instances in which the residua of an old pleurisy remain after a pulmonary infection. There may be no clinical signs of activity and roentgenologic examination may reveal only a pleural thickening or some elevation of the diaphragm, yet these patients will periodically notice abdominal distress which may simulate intra-abdominal disease. This occurs after



a period of prolonged overwork during which body resistance is depleted, or it may occur in the course of intercurrent infections.

With each recurring attack of pleural irritation the abdominal pain recurs. It may be extremely important to recognize this possibility in evaluating the cause of recurring vague abdominal distress for which no obvious intra-abdominal cause is demonstrable.

*Renal Disease.*—Chronic disease of the kidney with or without uremia may give rise to nausea, vomiting and symptoms of dyspepsia. In certain cases of prostatic obstruction and prostatic calculus the gastro-intestinal symptoms often are equal in importance to those referable to the genito-urinary tract. A careful history, thorough examination and essential laboratory tests usually clarify the diagnosis without much difficulty. We recently have been much impressed with the frequency of dyspeptic manifestations in cases of genito-urinary disease.

*Pelvic Disease.*—Pelvic disease does not, as a rule, produce symptoms referable to the upper part of the abdomen. The pain is usually in the lower abdominal quadrant. Nausea and flatulence may be associated symptoms. We saw recently a case in which the symptoms had suggested a recurrent attack of appendicitis; there had been leukocytosis, flatulence, nausea, vomiting, and elevation of temperature. An appendectomy had failed to produce relief. Drainage of a pelvic abscess which was performed later, was followed by prompt relief of symptoms.

*Hepatic Disease.*—Dyspeptic symptoms associated with ascites, enlarged liver, jaundice or hematemesis, alone or in any combination, should direct one's attention to the liver as the site of the trouble. Unfortunately, these prominent signs are usually late in their appearance. This is especially true in the compensated and preascitic stage of cirrhosis. Vague abdominal symptoms, such as discomfort, fullness and flatulence which occur at irregular intervals, may be present for months before the patient consults a physician. If a patient who complains of vague abdominal symptoms is a man who is past middle age and admits that he has used alcohol, and if examination reveals a slight enlargement of the liver, an epigastric

hernia, a hairless abdomen, and frequently a sallow or sub-icteric tint to the skin, one should suspect cirrhosis. Such tests as the van den Bergh test and the bromsulphalein test may be considerable help.

*Diseases Which Involve the Nervous System.*—Unfortunately, in a paper of this length it is impossible to deal with these diseases in sufficient detail. One need to pause only briefly to consider the complex mechanism of digestion and its intimate secretory and mechanical relationship to the sympathetic and parasympathetic nervous systems in order to understand how organic or functional disturbances of the nervous system may affect the digestive system. Dyspepsia may herald the onset of many of the diseases which involve the brain, the spinal cord, or the meninges. All physicians know that vomiting with or without nausea is an important symptom of an intracranial neoplasm. Careful investigation of the central nervous system, including ophthalmologic examination for choked disks and alterations of the visual fields, will usually enable one to determine the presence of disease of the central nervous system. We recently observed a patient who had been subjected to a gastro-enterostomy because of abdominal symptoms. Two years after the operation, which had failed to relieve the symptoms, a cerebral endothelioma had been removed. This had been the real cause of the symptoms. The gastro-intestinal symptoms which have recurred, erroneously had been attributed to malfunction of the gastro-enterostomy. The real cause of the symptoms is a tumor of the brain.

The crisis of locomotor ataxia may mimic many intra-abdominal diseases. This frequently is ushered in by a feeling of vague unrest in the upper part of the abdomen. Rumbling and gurgling occur throughout the abdomen. Pain may then develop and may rapidly become extremely severe. Nausea is extreme; vomiting not infrequently accompanies the pain. Often, there is a sensation of a band-like constriction encircling the abdomen. All of the symptoms may terminate rapidly without any subjective residual manifestations. At other times, however, the nausea and vomiting may persist for days; even the ingestion of small amounts of water may result in violent spasms of vomiting. The patient may become disturbingly dehydrated so that intravenous administration of fluids may

become necessary. At other times the attack is very mild and any of the mentioned symptoms in a minimal degree may be the sole manifestation of the disease. A carefully conducted neurologic examination will usually enable one to make a correct diagnosis.

*Pregnancy.*—It is not to be forgotten that one of the earliest symptoms of pregnancy is morning illness, nausea, and vomiting. The chief complaints of pregnant women as well as women who are passing through the menopause may be gastrointestinal in nature.

*Intoxications.*—Certain systemic intoxications, such as lead poisoning, alcoholism, excessive use of tobacco and coffee, and inhalation of noxious gases may cause gastric discomfort and even symptoms which suggest peptic ulcer.

*Alkalosis* which results from intensive treatment with alkalies may be heralded by anorexia, nausea, abdominal discomfort, distaste for milk, and later by headache, drowsiness, delirium, and coma.

*Endocrine Diseases.*—Certain patients who are suffering from various endocrine diseases may complain chiefly of dyspepsia. In the original description of Addison's disease, one may find the following statement: "The leading and characteristic feature of the morbid state to which I would direct attention are anemia, general languor and debility, remarkable feebleness of the heart's action, irritability of the stomach, and a peculiar change in the color of the skin." It now is possible to recognize the chronic stage of the disease, so well described by Addison, as well as the stage of crises which is characterized by anorexia, nausea, vomiting and diarrhea, circulatory collapse, and associated changes in the chemical composition of the blood.

It should be realized, however, that all the symptoms of the chronic phase of the disease may not be characteristic. Some patients complain chiefly of periodic attacks of vague indigestion which may be relieved by the ingestion of food or bicarbonate of soda. These symptoms may precede the anemia, languor and pigmentation. The patients may be treated for ulcer and such treatment may or may not produce relief. With progression of the disease the pigmentation is easily overlooked and during the attacks of nausea, vomiting and asthenia, pyloric

obstruction may be diagnosed. Some of these patients have learned to take unusually large amounts of sodium chloride.

Patients who have diabetic acidosis may complain chiefly of nausea, vomiting and abdominal pain. At times, the clinical picture may be so characteristic of acute or subacute appendicitis that in spite of the diagnosis of the acidosis (which is not always made) there is a temptation to do an appendectomy. Adequate treatment for the acidosis will quickly clear up the diagnosis. Failure of the patient to respond to adequate treatment probably means the presence of an acutely inflamed appendix. We saw one such case several years ago, but unfortunately the condition was diagnosed at necropsy.

*Deficiency Diseases.*—Gastric disturbances may precede the onset of characteristic symptoms of deficiency diseases, including pernicious anemia, sprue, and pellagra. Similarly, anorexia, sore tongue, indefinite gastro-intestinal disturbances not related to the ingestion of meals may be present for months before characteristic symptoms of pernicious anemia make their appearance.

*Migraine.*—A patient who has migraine may complain chiefly of nausea and vomiting, and occasionally he may complain of abdominal pain. These symptoms are more prominent in the mind of the patient than are the associated headache or such visual disturbances as scintillating scotoma. Careful inquiry will reveal that unilateral headache frequently is an associated symptom. Inquiry into the family history may reveal that other members of the family have had "sick headaches" or "bilious attacks."

*Allergy.*—Alimentary allergy is receiving confirmation in the literature as an explanation of some dyspeptic symptoms. One can become overzealous in this field and can waste valuable time on elimination diets before first ruling out other possible causes for the disturbance. There is no doubt that many people are allergic to certain foods. Symptoms may come on at once after the taking of foods or there may be a delay of several hours. We recall a doctor who had typical symptoms of ulcer, but who obtained relief after eliminating milk from his diet. A woman who was about to be operated on for cholecystitis volunteered the information that coffee caused a digestive disturbance. The elimination of coffee cured the chole-

cystic syndrome. Chocolate, eggs, wheat products, milk, strawberries and shell fish are the most frequent offenders, but almost any food may affect some people. If the patient keeps a food diary, the offending food may be readily recognized.

**Functional Dyspepsia.**—One is justified in making a diagnosis of a functional dyspepsia in about 25 per cent of all cases of dyspepsia. It can hardly be overemphasized, however, that this diagnosis should only be made after the exclusion of all other causes. Rather than place a stigma on these patients and in order to avoid an embarrassing situation for himself, the physician should keep constantly on the alert for further signs and symptoms that may point the way to another diagnosis. Many diseases in their early stages may masquerade as dyspepsia; therefore, a hasty diagnosis of a functional disorder may delay the recognition of the real trouble when definite signs and symptoms become manifest.

**Habit Dyspepsia.**—One of the most common varieties of dyspepsia is that resulting from improper habits of living and eating. A careful history will elicit the information that the affected patients not only eat too fast, too much, and at irregular intervals, but they are fond of highly seasoned foods, stimulating beverages, carbonated waters, coffee, fried foods, and so forth. They are frequently under high tension, smoke excessively, and keep irregular hours. The important diagnostic point in these cases is that the establishment of a saner way of living and regularity in hours, and the use of proper food cure the dyspepsia. The difficulty is that the relief of symptoms following the establishment of proper habits does not seem worth while to these patients, and they quickly return to their old habits of living. They are constantly seeking a new remedy or an easy cure, and usually have several "dyspeptic cures" in their homes or offices. As one patient said, he would rather live twenty years less, as he had been living with indigestion, than to live to a ripe old age in the manner in which he should live.

**Psychoneurotic Dyspepsia.**—This diagnosis is made after several complete reviews of the history, the asking of further questions, and an attempt to establish a more confidential atmosphere have failed to reveal the presence of organic disease. The dyspeptic symptoms complained of in these cases are only an abdominal manifestation of a disordered mental state.

It may be necessary to have the patients return to the office on repeated occasions. A relationship will be established between doctor and patient which will be more conducive to the tactful inquiry into certain intimate problems of the patient than that which was obtained at the first visit.

A past history of nervous breakdowns on the part of the patient or his relatives, a family history of insanity, marital disharmony, social conflicts, economic hazards, sexual problems, as well as the presence of an unstable emotional state are repeatedly denied until the patient has absolute confidence in the physician.

Eusterman listed the following characteristics as helpful in recognizing these patients: (1) The disturbance may be of long duration, yet complications or progression may be absent and the patient may be in a good nutritional state. (2) The symptoms vary in the region in which they appear; they are variable in degree and are frequently continuous. (3) There is lack of sequence which is characteristic of the majority of organic lesions. (4) The pain or discomfort, when present, is diffuse and often is referred unaccountably. (5) While the patient may complain bitterly of his disturbance or sensations during waking hours, the symptoms may be completely absent at night. (6) Intermittent digestive disorders are often coincident with, or follow, emotional stress. (7) Physical disability is frequently marked and is entirely out of proportion to the severity of the symptoms. (8) There is usually evidence of other stigmas of a psychoneurotic or hysteric personality.

These patients frequently are most anxious to have an organic basis for their complaints. They go from physician to physician until someone calls their disease a name which sounds important. They simply must have some subterfuge or some excuse for their disability or their complaints. Even though they may finally be convinced that their symptoms are functional, they are anxious that the family be left under the impression that there really was some basis for their complaints, as organic disease or the abuses to which they were subjected.

Finally, it must be admitted that the diagnosis of neurosis is a dangerous one. No one can deny that organic changes of a microscopic or biochemical nature may be present. The inability to recognize these changes or to measure variations

from normal physiologic activity does not mean that they do not actually exist. At least, it is safer to assume the possibility even though maintaining a confident and firm attitude toward the patient. No doubt many of the advances in the future will be directed toward establishing a definite organic etiology for these functional disturbances.





## PANCREATITIS

JAMES F. WEIR

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OUR interest in this subject was stimulated by the statement of one of our colleagues who said that he thought a correct diagnosis had only infrequently been made in cases of pancreatitis. When one thinks of pancreatitis one usually thinks of a pretty serious and often fatal condition. The textbook picture is one of catastrophe. We feel that many of the cases do not belong in that category. It has often been said that the gallbladder is a frequent source of the infection that precipitates infection in the pancreas. In several of the cases we wish to present there was apparently little trouble in the gallbladder. There has recently been reported in the literature some change in opinion in regard to the methods of handling patients with pancreatitis, and also a number of studies on enzymes. It is for these reasons that we would like to present the following four cases:

**Case I.**—Dr. Foley: The patient in the first case, a man aged thirty-five years, in August, 1919, had had an attack of epigastric distress and dull pain in the right upper quadrant of the abdomen. This attack had been followed by jaundice. Cholecystostomy had been performed elsewhere, and the gallbladder was said to have been infected. The patient had made a good recovery. In October, 1919, he came to the Clinic because of continued pain in the right upper portion of the abdomen, and because of epigastric distress which had been worse three hours after meals and had not been relieved by food. Dietary management was advised. The patient improved and remained well until 1927 when he had two chills, with fever, epigastric distress, gas, and belching. Two days later he noticed some jaundice. This cleared after a few days. In 1928 the patient had repeated attacks of right upper ab-

dominal distress, chills, fever, gas, constipation and clay-colored stools. In November, cholecystectomy was performed, elsewhere. He improved for two weeks after operation, but the symptoms recurred. These attacks continued at intervals of one to four weeks. In March, 1931, a T tube was placed in the bile duct. The surgeon told him that the common duct was merely a fibrous cord. Fifteen days after operation an abscess of the liver developed and was drained. On June 10, 1931, another exploratory operation was carried out, elsewhere. The T tube was not removed. Subsequently, the jaundice disappeared and the stools became normal. The patient continued to have "sour stomach" occasionally and attacks of dull epigastric pain lasting two days.

In the spring of 1932, the patient had a mild chill, followed by fever which lasted only two days but reappeared the following September. This attack was associated with dark urine and jaundice. The condition cleared after a few days, but the patient continued to have some epigastric distress for which he came to the Clinic, October 26, 1932. At that time a roentgenogram of the thorax revealed marked irregularity of the diaphragm on both sides. Roentgenograms of the gallbladder, without dye having been given, and of the stomach and duodenum, were negative. The laboratory findings were as follows: galactose tolerance test, negative; serum bilirubin, 2.2 mg. per 100 c.c. (direct reaction); hemoglobin, 12.6 gm. per 100 c.c., and erythrocytes 4,030,000 and leukocytes 6,100 per cubic millimeter of blood. A diagnosis was made of intermittent obstruction of the common duct, the patient was hospitalized, and medical treatment was given.

On May 4, 1933, the patient returned to the Clinic and stated that he had been troubled with several attacks similar to previous ones; he had become considerably jaundiced just a few days prior to this visit to the Clinic. At this time the laboratory findings were as follows: hemoglobin, 11.5 gm.; erythrocytes 3,750,000 and leukocytes 3,600 per cubic millimeter; serum bilirubin, 6.8 mg. (direct reaction), and the galactose tolerance test, negative. Urinalysis gave negative results except that the urine contained bile. The diagnosis of intermittent obstruction of the common duct was again made, together with that of jaundice and secondary biliary cirrhosis.

Exploration was performed May 30 by Dr. Walters. The liver was found to be cirrhotic, grade 4. Every portion was involved and was covered with hobnail nodules. In view of this, and of the presence of bile in the duodenum, it was thought unwise to dissect the mass of adhesions in search of the common duct; a specimen of the liver was taken for biopsy and the abdomen was closed. The patient made an uneventful recovery and was dismissed June 24, 1933. He then remained fairly well until October, 1933, at which time there was recurrence of chills and fever, and of colicky pain in the right upper portion of the abdomen. The pain was projected through to the back and was associated with nausea, vomiting and fluctuating jaundice. These attacks occurred at weekly intervals. In August, 1934, he began to have diarrhea. He had from two to twelve stools a day; they were gray, were not greasy or foamy and did not float.

The patient returned to the Clinic March 7, 1935. He was hospitalized immediately because of severe attacks of pain in the right upper quadrant of the abdomen; morphine was required for relief. These symptoms and the diarrhea continued unabated until he left the hospital March 12. On this last visit he was found to be moderately emaciated, and a marked degree of jaundice and a fairly marked degree of clubbing of the fingers were present. He had a ventral hernia and enlarged veins on the abdominal wall. On deep inspiration the edge of the liver could be felt about 2 cm. below the costal margin. Moderate ascites was present. There was slight edema of the ankles. The blood pressure was 118 mm. systolic and 72 mm. diastolic. The laboratory data were as follows: March 7, hemoglobin, 8.45 gm.; erythrocytes, 3,130,000 and leukocytes, 2,900; March 9, hemoglobin, 8.1 gm. and erythrocytes, 3,120,000 and leukocytes, 4,100. There was slight macrocytosis. The serum bilirubin on two occasions was 12.0 mg. and 11.0 mg. per 100 c.c., with a direct reaction. The blood calcium was 6.7 mg. and blood phosphorus 1.5 mg. Blood sugar was 120 mg. per 100 c.c. The galactose tolerance test was negative. The serum protein was 5.6 mg. On several occasions the stools were positive for bile. The roentgenologist reported the stomach and proximal portion of the jejunum to be negative; the lower part of the jejunum and the ileum and colon had a fine,

dominal distress, chills, fever, gas, constipation and clay-colored stools. In November, cholecystectomy was performed, elsewhere. He improved for two weeks after operation, but the symptoms recurred. These attacks continued at intervals of one to four weeks. In March, 1931, a T tube was placed in the bile duct. The surgeon told him that the common duct was merely a fibrous cord. Fifteen days after operation an abscess of the liver developed and was drained. On June 10, 1931, another exploratory operation was carried out, elsewhere. The T tube was not removed. Subsequently, the jaundice disappeared and the stools became normal. The patient continued to have "sour stomach" occasionally and attacks of dull epigastric pain lasting two days.

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The patient returned to the Clinic March 7, 1935. He was hospitalized immediately because of severe attacks of pain in the right upper quadrant of the abdomen; morphine was required for relief. These symptoms and the diarrhea continued unabated until he left the hospital March 12. On this last visit he was found to be moderately emaciated, and a marked degree of jaundice and a fairly marked degree of clubbing of the fingers were present. He had a ventral hernia and enlarged veins on the abdominal wall. On deep inspiration the edge of the liver could be felt about 2 cm. below the costal margin. Moderate ascites was present. There was slight edema of the ankles. The blood pressure was 118 mm. systolic and 72 mm. diastolic. The laboratory data were as follows: March 7, hemoglobin, 8.45 gm.; erythrocytes, 3,130,000 and leukocytes, 2,900; March 9, hemoglobin, 8.1 gm. and erythrocytes, 3,120,000 and leukocytes, 4,100. There was slight macrocytosis. The serum bilirubin on two occasions was 12.0 mg. and 11.0 mg. per 100 c.c., with a direct reaction. The blood calcium was 6.7 mg. and blood phosphorus 1.5 mg. Blood sugar was 120 mg. per 100 c.c. The galactose tolerance test was negative. The serum protein was 5.6 mg. On several occasions the stools were positive for bile. The roentgenologist reported the stomach and proximal portion of the jejunum to be negative; the lower part of the jejunum and the ileum and colon had a fine,

granular appearance that might have been caused by food and barium.

DR. WEIR: This patient represents one of the catastrophes of disease of the biliary tract. The reason we are presenting the case is that since the patient's last visit to the Clinic diarrhea developed. We feel that this diarrhea is of pancreatic origin. The stools contained excessive amounts of fat, so-called steatorrheic stools. There was evidence of portal obstruction—edema, ascites, and distended veins in the abdomen. The persistence and severity of pain at the time of the last visit was possibly the result of an associated pancreatitis.

DR. GEORGE BROWN: Will you just restate the sequence of events as to where the pancreatitis stood in relation to what had been done in the past?

DR. WEIR: The patient had had four or five operations prior to exploration performed here in 1933, when, because of extensive cirrhosis and adhesions, the surgeon did not feel justified in dissecting down to the common duct. The patient possibly has a stone in the common duct, but cholangitis, cirrhosis and adhesions are certainly present and with pancreatitis can explain the patient's symptoms. Last fall diarrhea developed and there was loss of weight and pain, more severe than in the past. This is probably the time that pancreatitis developed.

DR. BROWN: Do you think the operative procedures and disease of the biliary tract are of secondary importance to the pancreatitis?

DR. WEIR: No. We cannot be sure how much the operations had to do with the patient's condition. If he had had a stricture or stone in the common duct, either could have played a large part in cirrhosis. On the other hand we know a patient can have cirrhosis with pain and without stones in the common duct. He can have attacks of colic, jaundice and so forth when the liver alone is diseased. In this case obstruction of the common duct probably was present and the liver and pancreatic changes were secondary.

DR. HELMHOLZ: He was relieved of jaundice when the fistula occurred, wasn't he?

DR. WEIR: Temporarily.

DR. HELMHOLZ: Did he have jaundice after that?

DR. WEIR: Yes. He has had it constantly for the last six or eight months.

**Case II.**—Dr. Foley: The next patient, a woman, twenty-eight years of age, had always been well until March, 1934. At that time a rather sudden attack of pain had developed in the right upper quadrant of the abdomen and this pain had been projected to the back and to the right shoulder. She had become jaundiced and had remained so. She had had chills, but not much fever, for about a week and had then recovered. She had had no qualitative distress from taking of food. She had continued to have an attack about once a week until December, 1934. There had been no jaundice during the time between attacks. On December 24, 1934, the patient's husband had noticed that she had a slight icteric tinge. Within the following few days she had become more jaundiced and had had several severe attacks of pain in the right upper quadrant of the abdomen.

Since that time the attacks had become more frequent, occurring every four or five days to a week. Throughout January and February she was confined to her bed. She had a fever, the temperature ranging from 99° to 103° F. The pulse rate was rapid through it all, ranging from 120 to 150 beats per minute. The jaundice fluctuated with the attacks. With each attack the pain was projected through to the back and was typical of a biliary type of pain. With this illness a mid-epigastric mass appeared, but it subsequently subsided. The patient had two tarry stools, but without having received medication of any kind which might have accounted for their appearance. She lost about 50 pounds (22.7 kg.). Her family physician noted glycosuria a few times. Other than that the history was negative. Examination at the Clinic gave negative results except for tenderness in the epigastrium grade 2, and slight jaundice.

DR. WEIR: The patient was obese. Her weight before she became ill was more than 200 pounds (90.7 kg.). She was younger, however, than the usual patient with acute pancreatitis, being at the time of admission only twenty-eight years old. She has had attacks of pain in the right upper quadrant of the abdomen similar to biliary colic which suggests the presence of

gallstones. Her referring physician sent along a letter describing her illness in January and February, during which time she had had severe pain requiring morphine for relief. The fever had persisted and a mass had developed in the epigastrium which he thought was an enlarged pancreas. She had been very ill at the time and had lost 50 pounds.

The history of a mass in the epigastrium, persistence of fever, pain and jaundice was practically diagnostic of acute pancreatitis. The patient had slight anemia and the serum bilirubin was 4.5 mg. The serum lipase was normal. Dye retention was graded 4; we would expect that with a history of jaundice over that length of time. The patient was operated on a few days later and the pancreas was found to be markedly enlarged and swollen. There were no stones in the biliary tract. The gallbladder was distended and edematous but was not otherwise diseased; it was removed and the common duct drained.

The prognosis in this case is rather uncertain. Whether prolonged external drainage of the common duct and keeping the patient's weight down and maintaining her in good health will help is problematic.

DR. BROWN: What is the mechanism of the periodic attacks of pain?

DR. WEIR: They are probably caused by acute exacerbation of the pancreatitis.

DR. BROWN: Is distention of the gallbladder due to edema or to backing up of bile?

DR. WEIR: I believe enlargement of the pancreas causes obstruction of the common duct, with secondary distention of the gallbladder. Edema plays a rôle in the pancreatic enlargement.

QUESTION: Do you think it is an infectious condition?

DR. WEIR: I think probably it is. Dragstedt did some work on this and found that *Bacillus welchii* was a common offending organism. Some men recommend the use of *Bacillus welchii* antitoxin.

DR. ALLEN: Why take out the gallbladder?

DR. WEIR: There may be some difference of opinion as to the advisability of that procedure.

DR. BROWN: How long do these attacks last?



DR. WEIR: This particular acute attack lasted two months.

QUESTION: Did the swelling last?

DR. WEIR: Yes. The pancreas is still swollen, although it has decreased in size so that it could not be palpated through the intact abdominal wall.

QUESTION: Have you made microscopic examinations in cases of pancreatitis?

DR. WEIR: Yes, but seldom as a surgical biopsy. Pathologic examinations are usually on necropsy material. An inflammatory reaction is found throughout the pancreas. Evidence of edema and fat necrosis may be prominent.

QUESTION: Does obstruction take place in the pancreatic ducts?

DR. WEIR: In some cases it does, but in others it doesn't.

QUESTION: How large did the surgeon say the pancreas was?

DR. WEIR: He said it was twice the normal size. It had decreased in size before operation so that we could not feel it. The patient was still obese; she weighed 160 pounds (72.6 kg.).

DR. FOLEY: One other thing I forgot to mention was that the concentration of blood sugar was 120 mg. per 100 c.c.

DR. WEIR: Glycosuria is frequently found in acute pancreatitis. In other cases a diabetic sugar tolerance curve may be found and, in later stages, a well-marked diabetes may appear.

**Case III.**—Dr. Foley: The patient in the third case, a man aged forty-three years, had first come to the Clinic August 8, 1932, with his wife. He had decided to be examined while he was here because for about two years he had had periodic attacks of burning pain in the epigastrium. These attacks had come on two to three hours after meals. Food and soda had given relief. There had been no pain at night nor projection of pain through to the back.

Examination revealed infected tonsils and some infected teeth. There was moderate tenderness in the epigastrium. Urinalysis gave negative results. The value for hemoglobin was 16.7 gm. per 100 c.c. of blood, and erythrocytes numbered 4,540,000 and leukocytes 14,200 per cubic millimeter. Analysis of the gastric content revealed total acidity of 44 units,

free hydrochloric acid of 32 units and a total quantity of 50 c.c. A roentgenogram of the stomach disclosed marked hypertrophy of the mucous membrane suggestive of gastritis. A tentative diagnosis was made of chronic gastritis. An ulcer type of regimen was prescribed and the patient was advised to have all foci of infection removed. He was then dismissed, and was asked to return in three months for further observation.

The patient returned January 23, 1933. At that time leukocytes numbered 11,000 per cubic millimeter. Analysis of the gastric content revealed a total acidity of 40 units, free hydrochloric acid of 28 units, a total quantity of 50 c.c. Fresh blood, grade 3, was present. A roentgenogram of the stomach again revealed marked hypertrophy of the mucous membrane; the duodenum appeared to be normal. The patient was dismissed but returned again October 12, 1933, at which time analysis of the gastric content revealed a total acidity of 52, free hydrochloric acid of 42 and a total quantity of 60 c.c. The patient had improved, but he still had periods of discomfort in the region of the epigastrium of two or three days' duration. This discomfort was followed by three or four days of freedom from symptoms. The results of general and roentgenographic examinations of the stomach were the same as on previous visits.

The patient was reexamined at the Clinic February 9, 1934, and said that the distress had remained unchanged until January 20, at which time severe, diffuse soreness throughout the abdomen had developed and had been associated with a temperature of 100° to 101° F. He was placed on ulcer treatment and, after three or four days, this trouble disappeared. The patient continued to suffer attacks of epigastric pain, occurring at 2 to 4 a. m. A roentgenogram revealed hypertrophy of the gastric mucosa and a perforating ulcer high on the posterior wall. The abdomen was explored February 12 by Dr. Judd, but he did not find any evidence of a perforating gastric ulcer. Marked pancreatitis and diffuse gastritis were present. The appendix was chronically inflamed and was removed. The gallbladder and liver appeared to be normal. The patient made an uneventful recovery from the operation.

The patient returned to the Clinic June 11, 1934, and stated that the pain had lost some of its relationship to meals and had been more constant. He had also noticed exacerbations of his

distress on two occasions following extraction of teeth. In May there had been some associated aching pain in the left lumbar region and on several occasions the stools had been light colored and the urine dark, without the appearance of noticeable jaundice. Erythrocytes at this time numbered 4,780,000 and leukocytes 7,600 per cubic millimeter. Gastric analysis revealed a total acidity of 34 units and free hydrochloric acid of 22 units, the total quantity being 50 c.c. The gastric content contained fresh blood, grade 1. The value for serum lipase (olive oil substrate) was 4 c.c. of twentieth normal sodium hydroxide per 100 c.c. A roentgenogram of the stomach revealed marked hypertrophy of the gastric mucosa. The patient was advised to continue on an ulcer type of regimen and to have his infected teeth and tonsils removed.

The patient returned to the Clinic in March, 1935. Since his previous visit he had had four or five attacks of epigastric pain and numerous occasions when the stools were light colored and loose. The value for hemoglobin at this time was 15.9 gm. per 100 c.c. of blood; erythrocytes numbered 3,870,000 and leukocytes 7,200 per cubic millimeter. Gastric analysis revealed a total acidity of 44 units, free hydrochloric acid of 30, and a total quantity of 30 c.c. The value for serum lipase was 7.9 c.c. of twentieth normal sodium hydroxide per 100 c.c. A roentgenogram of the stomach again revealed marked hypertrophy of the gastric mucosa, but there was no evidence of ulceration. Gastroscopic examination was performed by Dr. H. J. Moersch and nothing more than hypertrophied gastric mucosa was noted. The continuance of medical treatment was advised.

DR. WEIR: In June, 1934, the serum lipase was normal, about 2 c.c.; in March it was 7.9. That is the highest we have on record at the present. This is the interesting thing from the laboratory standpoint. You may ask what the significance of the hypertrophic gastric mucosa is. So far we do not know its significance. The question may also be asked whether the gastritis or hypertrophy had anything to do with the pancreatitis, or vice versa. I do not believe it did. I think the hypertrophy of the mucous membrane was a more or less incidental thing. The perforating ulcer found on roentgenographic examination probably resulted from the inflammatory

process in the pancreas having involved the posterior wall of the stomach. This case illustrates that type in which a great deal of pain is not manifested. The patient has had no jaundice. There has been some progressive loss of weight.

QUESTION: Does pancreatitis have any relation to focal infection?

DR. WEIR: I do not know.

DR. HELMHOLZ: I notice that twice you recommended removing the tonsils and teeth, but that nothing was done about it.

DR. WEIR: Here we are on debatable ground, and I do not know how you are going to settle the debate.

**Case IV.**—Dr. Foley: The patient in the fourth case, a man aged thirty-six years, was sent to hospital in an ambulance, March 9, 1935. He had always been in good health until twelve years previously when he had had cramps in the right upper quadrant of the abdomen followed by jaundice which had lasted for about a week. There had been marked distention of the abdomen for which castor oil and other laxatives had been given. The patient had been a fairly heavy drinker of alcoholic beverages for the last eight or ten years. He was a solitary drinker and always had liquor with him; he drank one or more pints of whiskey a day. Eight years ago he had begun to have periodic attacks of pain in the upper portion of the abdomen, associated with chills, fever, sweats and constant upper abdominal soreness. Each attack had lasted about four days, with one day of warning during which the patient had had anorexia and abdominal distention. The attacks had occurred about every six weeks. The pain had been felt first in the epigastrium; it had then been projected across the abdomen to the right and left and to the back, between the shoulders. It frequently had been sharp and severe and as many as three hypodermic injections of morphine in one hour have been required for relief. The fever, chills and sweats usually had continued for several days after the pain had disappeared. The patient had gained most relief from the attack by assuming a bent-over, crouched position. These attacks had continued until one year prior to his admission, had then stopped, but had recurred six weeks before his admission. Seven years before admission exploratory laparotomy

had been performed, elsewhere. A preoperative diagnosis of ulcer had been made but an ulcer had not been found at operation. The surgeon had noted that the pancreas was indurated and hard. The patient had gone to the hospital for three or four days with each of these attacks of pain, but no further treatment or investigations had been carried out in those seven years. The patient knew definitely that he had had diabetes mellitus for six weeks; his nurse stated that he also had had polydipsia and polyuria, and that he had lost weight for nearly a year. He had been taking 40 to 70 units of insulin daily for the last six weeks. His appetite had remained good. There had been considerable bloating and distention after meals. His bowels had moved regularly but the stools had been greasy, bulky, foamy and contained undigested food. He had lost 25 pounds (11.3 kg.) in the past year.

Examination revealed the patient to be undernourished, grade 2. The abdomen was not distended but was tense. No masses were present. The laboratory data were as follows: The urine was negative, the value for hemoglobin was 13.3 gm. per 100 c.c. and erythrocytes numbered 4,100,000 and leukocytes 7,900 per cubic millimeter. There was no evidence of macrocytosis. The concentration of blood urea was 20 mg. and that of blood sugar 163 mg. per 100 c.c. The value for serum bilirubin was 1.0 mg. and the reaction was indirect. Serum protein was 7.24 gm., and the albumin-globulin ratio 1.6:1. A test of hepatic function gave negative results. The hippuric acid test was negative, 5.22 gm. of hippuric acid being excreted. There was 4.81 mg. of serum phosphorus per 100 c.c. The value for serum lipase (olive oil substrate) was 1.5 c.c. of twentieth normal sodium hydroxide per 100 c.c. There was no activity of amylase and trypsin in the duodenal content either before or after administration of magnesium sulfate. The flocculation test for syphilis gave negative results. Roentgenograms revealed a normally functioning gallbladder. Many concretions were present in the pancreas. There was slight hypermotility of the small bowel; the mucosal pattern was normal.

DR. WEIR: Roentgenograms of the gallbladder gave evidence of normal function. It was found that there was some calcification in the region of the head of the pancreas. Further

roentgenograms were reported as giving evidence of multiple, extensive pancreatic lithiasis. The question comes up as to whether there are multiple calculi in the duct or not. After discussing this with the roentgenologists it was felt that extensive calcification and not stone in the pancreatic duct was present throughout the pancreas, the result of previous inflammation. Calcification takes place secondarily during the process of healing after fat necrosis. In this case exploration also was done; the gallbladder was drained; it was tense but there were no stones. The common duct was opened and no stones were found; a tube was put in for prolonged drainage. This case illustrates the development of pancreatic insufficiency after the development of pancreatitis, and that is manifested by the steatorrhea, loss of weight and by the more recent development of a diabetic syndrome.

QUESTION: Is that a common complication?

DR. WEIR: No, not very common. These patients are all young and pancreatitis is frequently considered as afflicting people a good deal older. Only one of the four was obese. I am going over some figures that Dr. Bannick has collected in regard to various points in a series of forty-seven cases. He divided them into hyperacute cases, thirteen, and acute cases, thirty-four. The hyperacute cases probably correspond to the old acute, hemorrhagic pancreatitis, with a rapidly fatal illness. Twelve of these thirteen patients died. In the thirty-four acute cases a diagnosis of pancreatitis was made correctly in only one case. It was suspected in four. Of the whole group of forty-seven cases, in twenty-seven the diagnosis was considered to be probable acute cholecystitis, in eight cases perforated ulcer, in four cases intestinal obstruction, in one case appendicitis, and in one case colic; in the remaining cases the diagnosis was indeterminate, and the distribution by sex was about equal. The patients' ages varied from twenty to seventy years. Seventy-nine per cent were obese. About 14 per cent had had previous dyspepsia but no attacks. Ten per cent had had no previous attacks at all.

In 85 per cent of the cases the attacks were associated with gallstones; some investigators give this figure as 45 to 50 per cent. It is the most frequently associated disease. The pain usually is sudden, acute, very severe and prolonged, and mor-

phine is frequently required for relief. The pain is situated in the upper part of the abdomen, in the right upper quadrant more frequently than in the left, although it was present in the left upper quadrant in a number of cases. The pain is projected posteriorly. Vomiting is common; it was present in twenty-five of the thirty-four acute cases. Tenderness is usually present. The rigidity which is present occurs largely in the right upper quadrant; it is different from that of perforated ulcer, lacking the board-like quality found in ulcer. Ileus was present in a few hyperacute cases and was marked; in the so-called acute cases it was not often present. The features of shock were most common in the hyperacute cases. Jaundice was present in thirteen of the hyperacute and in eleven of the acute cases. That symptom would help to distinguish pancreatitis from perforated ulcer. Glycosuria was found in 3 per cent of the hyperacute cases but in none of the acute cases. Fever was present in all but two cases. Leukocytes were increased to from 13,000 to 29,000, the usual increase being 17,000 per cubic millimeter.

So far as the studies on enzymes are concerned, we have not been doing any duodenal drainage to determine the enzymes except in the occasional case. We have been doing the serum lipase test, however, and a short time ago Dr. Comfort reported on 162 of these tests. One hundred and thirty patients were without known pancreatic disease, the value for lipase in 119 of these being less than 2 c.c. of twentieth normal sodium hydroxide per cubic centimeter of serum. In the thirty-two cases in which pancreatic disease was present, the value in 41 per cent of them was more than 2 c.c. There were twelve cases in which it was more than 3 c.c., nine of the patients having pancreatic disease and the other three diseases with which pancreatic disease often is associated: carcinoma of the gall-bladder, peritonitis and toxic hepatitis following pneumonia. Comfort has gone over subsequent cases in which the value for serum lipase has been determined and he has a series of more than 700 cases. His feeling is that a serum lipase of more than 2 c.c. is usually indicative of pancreatic disease.

As has been said, the highest value for serum lipase we have on record is 7.9 c.c. In the chronic cases apparently there is not much elevation. Elevation occurs in the acute

cases. So far as a study of the duodenal enzymes are concerned, the report of a committee at the last meeting of the American Gastro-enterological Association on the frequency with which the tests were used by members of the Association is of interest. They sent out 135 questionnaires and got replies from eighty-three members. Of these, thirty-seven members do not perform the tests. Duodenal drainage for trypsin was used by twenty-seven, for lipase by twenty and for amylase by twenty-three. So it is not used commonly even by members of the Association, the members of which are interested in pancreatic disease. The consensus of opinion was that in cases in which there was absence of pancreatic enzymes, the condition was caused by obstruction of the pancreatic duct. It was quite definite, also, that in sprue there was a decrease in pancreatic enzymes. The Committee felt that the difficulty in these determinations was pretty much a technical one. The question of the proper method of collecting specimens was a large factor.

Going back to our cases; so far as prognosis is concerned, it is uncertain. I think the first and last patients are near the end stage. They have pancreatic insufficiency, so far as digestion of food is concerned and the last patient has diabetes.

QUESTION: Do you think we are missing many of these cases?

DR. WEIR: I think we are missing quite a few of them. In subacute cases the condition is thought to be gallbladder colic.

QUESTION: Is there any difference in the pain?

DR. WEIR: Yes; in pancreatitis it is more persistent.

QUESTION: What do you say about the differential diagnosis?

DR. WEIR: It is very difficult to make a differential diagnosis. I think most of the men at the Clinic have not been successful in making one.

QUESTION: Did I understand you to say that in a series of thirty-four cases the diagnosis was correct in only one?

DR. WEIR: Yes. In the group of hyperacute cases there were a greater number of correct diagnoses.

QUESTION: Do they average better now?

DR. WEIR: I do not know. This is rather a flexible classi-



fication. As I have said, what Dr. Bannick calls hyperacute, is what was called the acute hemorrhagic case. Furthermore, I think the general tendency is away from surgery during the acute stage of the illness, such as in the second case we presented.

The physician at home found a mass but he did not advise surgery. The suction drainage apparatus is used for the stomach and glucose and saline solutions are administered intravenously; sometimes insulin is added to the treatment. These patients are treated as if they had intestinal obstruction. Wangensteen particularly advises that form of treatment. In the stages of suppuration it may be necessary to open and drain the pancreas, but that usually comes later, after the patient is over the shock of the original illness. The mortality in the acute stage is from 60 to 75 per cent. Those figures are pretty much for the hyperacute or the more severe acute cases.

QUESTION: Has pancreatitis occurred in children?

DR. AMBERG: We have never seen it and I have looked for it.

DR. HELMHOLZ: There are some cases of pancreatitis, with steatorrhea, in children, but they are very few and far between. Hess has reported some cases that had the picture of celiac disease, with marked sclerosis of the pancreas, but that was something different. Parker of San Francisco had one case. This is reported in the recent *Journal of Pediatrics*.



## CONSTIPATION

PHILIP W. BROWN

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WHAT more can be said about constipation? The earliest records of man indicate that the two "C's," civilization and constipation, have carried along together to the present time. It is unlikely that the Ebers' Papyrus had as large a circulation among the ancient Egyptians as have our present-day papers, billboards, and magazines, but both early and recent writings stress the problem of constipation. The enemas and irrigations of our day have their counterpart in the enemas of ancient times, when the apparatus consisted of a leather bag or the bladder of an animal, to which was fitted a leg bone of a fowl or a small horn, as the enema tip. It is interesting that the early American Indians used a type of enema outfit similar to that recorded as having been used in early Chinese medical practice; this is, incidentally, another small item tending to support the idea that the origin of the Indian was the Yellow Race of Asia. Much later, in the seventeenth and eighteenth centuries, there were long, verbose diatribes on the use of the physick, the eccoprotic, and the purge. The season of the year, the position of the moon, the stature of the patient and so forth, had to be considered; yet these treatises are not more incentives to smile than are some of the more recent articles on auto-intoxication, spastic constipation, atonic constipation, constipation of infants, constipation of the aged and so forth. The enthusiasm for buttermilk, and later for acidophilus milk, have their counterpart in the writings of Paulus Aegineta, about 600 A. D., in which use of whey and sour milk was advised.

Hence, there is an ideal for which to strive, namely, a sensible understanding and a regimen for the management of a bodily function which has been faulty since the dawn of civilization. Many physical attributes, both external and internal, may be apparent in the species "*Homo sapiens*," yet

many of the recommendations for the management of constipation would indicate that he has been misnamed. One of the lessons hardest for both physician and patient to learn has been that, in spite of some similarities, the past, present, or future of no two people are exactly the same. The only possible exception might be in the case of apparently identical twins. Certain principles and working plans may be suitable as a start but the program must be altered to suit the individual; stock sizes of clothes may fit the bodies of many, but even then they are rarely as satisfactory as made to order clothes.

#### APPROACH TO THE PROBLEM

In view of this conception of constipation, it is obvious that the first necessity is evaluation of the individual and of what he means by "constipation." Commonly, he means a condition in which either bowel movements occur infrequently or the volume of the stools is insufficient. Some patients have become imbued with the idea that more than one stool a day is essential to good health. Others may have taken a laxative one or more times a week to "clean out"; evidently this is a heritage from former ages, for in Hindu writings of about 800 B. C. taking of a purge at regular intervals is advised. Still others have lived on a concentrated diet of meat, bread, tea, eggs, and so forth, and then become concerned that they pass only a small, dry stool every two or three days.

There seems little logic in endeavoring to classify types of constipation. The influence of early roentgenographic studies, in which the shadow seemed to indicate atonic or spastic states of the colon, has been as difficult to shake off as have the ideas originating in the same era, concerning dropped stomachs and dropped colons. The more inaccessible the organ, the more mystery that exists as to its function. How often the patient, with eyes dilated, tells of the bulky mass being propelled and churning its way like a battering ram through his sluggish bowel, or how often the woman tells how her tender colon has been scratched and rubbed by coarse foods, just as sandpaper would tear the face.

What is the physiology of the normal colon? There is enough sound knowledge to enable physicians to explain this

simply to their patients. Practically all of absorption of food has occurred before the residue reaches the cecum. In the right half of the colon, most of the water is then absorbed and the material begins to pass on into the left half of the colon in four to twelve hours, although even this figure varies widely. The left half of the colon is the storage space, or fecal reservoir, which normally empties in part at fairly regular intervals.

A sincere endeavor has been made to establish an upper limit to time, beyond which the interval required for passage of material through the bowel could be considered abnormal. Studies carried out by Alvarez and Freedlander indicate that there is a wide variation in the rate at which feces pass through the bowel. They used small beads and in further experiments measured the daily fractions of a barium meal excreted on successive days. About four days were required for excretion of 75 per cent of the beads or barium. In the same study, these investigators observed that if the colon was thoroughly emptied, either by a cathartic or because of diarrhea, there were no movements, or very small movements, for the next two or three days, or until the colon had filled again. It therefore is unphysiologic to empty the colon; normally only the terminal accumulation is pushed out at one time. This idea is important in the individual problem. Some colons are large, without megacolon actually being present; some absorb more fluid than others, leaving a drier, harder mass. The "wiring" of the colon, that is, the nerves and the stimulation mediated by them, differ with different individuals, and not only this but the control of the colon through the voluntary nerves also differs. The material from the ileum seems to be pushed into the cecum and ascending colon. At intervals in the day, mass movements occur which force the fecal content into the descending colon and rectum. This impulse, the gastrocolic reflex, seems often to be initiated by ingestion of food and when the impulse is fairly active, it explains why some people have a bowel movement after each meal. In a larger group, this mass movement seems to need to be repeated until sufficient residue has been pushed down to the rectosigmoid to initiate the desire to go to stool. If this desire is unheeded, some of the feces is carried back to the transverse colon. The neuro-anatomic trigger point in the rectosigmoid is not demonstrable. From experi-

ence, it is known that the rectum is normally empty except just before evacuation. Also, when the proctoscope is inserted into the rectosigmoid the patient usually announces that his bowels are going to move although the examiner can see that fecal material is not present at the moment. Other evidence that there is such a trigger zone is that if the rectosigmoid is resected, patients find it difficult to move the bowels, even though the channel is patent. This may likewise explain why, in some cases in which ileosigmoidostomy has been performed, constipation supervenes instead of the to be expected looseness of the stool. A physiologic, not an anatomic, block occurs.

#### SYMPTOMS OF CONSTIPATION

Are there symptoms attributable to failure to evacuate a certain amount of feces every day or two? Certainly, volumes have been written and advertisements have been poured forth on the dire result of faulty elimination. When all other factors have been eliminated, the sluggish colon has been blamed for arthritis, epilepsy, malignancy, and so forth. As this is being written (autumn of 1936), newspapers carry dispatches on the discovery of a cure for arthritis by means of a drug which will overcome or neutralize the poisons absorbed from a stagnant colon, evidently on the assumption that they are the cause of arthritis. There seems no doubt that most reasonable people, and who we or they are had best not be defined, insist they feel better, enjoy their meals more, and sleep better when their bowels move regularly. Closer analysis usually reveals that such people live fairly regular lives, that they eat, work, play, and sleep in a balanced, orderly fashion. They may work hard and deal with difficult mental problems but they, wittingly or unwittingly, have learned to spend only so much of themselves and always have something left over. When there intervene undue sorrows, irregular hours for sleeping and eating, or dissipation, so that there is nothing left over, then they begin to note irregular digestive disturbances and often sluggish intestinal action. All physicians know the occasional healthy, happy, competent person who defecates only twice a week, in contradistinction to the thin, nervous, frantic soul who purges or sluices his bowel one or more times a day with the idea that the bowel causes his sorrows. The extreme example of this

second type is the patient who exemplifies the "colon obsession neurosis," than which there is nothing more pathetic nor more exasperating. Likewise, is it not impressive that the patient with megacolon, who has a bowel movement only once a week, or even once in several weeks, has no particular digestive trouble? Their concern might be held to be more a cosmetic one, as the distended colon makes the abdomen more and more prominent.

Have we not tended to stress the symptoms of sluggish intestinal action, rather than to recognize it as merely part and parcel of the general social-economic struggle? It seems to me, in reading the ancient and medieval writings, and comparing our present-day patients with those described there, that constipation is an expression of disordered living, be it in the periods of famine of primitive peoples, when they had not sufficient food to make fecal residue, or be it exemplified by our modern peoples whose nervous systems are torn by the complexities of life. I have often wished that it were as easy to explain this to patients and to have them accept it readily as it is to inoculate them with the diagnosis of spastic colitis. More than twenty years ago an intelligent but very high-strung woman had been told by two of the most prominent surgeons of our period that she had spastic colitis. All these twenty years, enemas from one to ten times a day had been employed to wash out the poisons and to lave the lining of her supposedly diseased bowel. I had the temerity to suggest gradual discontinuance of the enemas and giving the bowel a chance. The reply was to be expected, "Well, I'd have you know Dr. — and Dr. — made my diagnosis, and if that is all you know there is no use wasting your or my time." The last part of her comment is correct; namely, it is usually a waste of the physician's time to "undiagnose" this condition for such a patient.

Although I feel strongly that constipation is a manifestation of faulty living, yet it is necessary to bear in mind that there are symptoms attributable to the condition. Most commonly, there is vague dyspepsia, flatulence, and back pressure from the bowel to the stomach. The appetite is poor and the tongue coated. This may be because the ileum has difficulty in forcing its content into the overloaded bowel, with re-

sultant increase in the frequency of reversed peristaltic waves in the small bowel. In some cases, this distention of the right half of the colon leads to tenderness in the right side, which has so often resulted in the diagnosis of chronic appendicitis and in unfairly crediting surgical operation with failure.

### DIAGNOSIS

All preceding remarks, and those in the rest of this article, are predicated on the fact that the patient does have constipation. The fact must be established not only by the patient's history but by thorough and conscientious examination. The occasional streaks of blood on the stool are probably attributable to hemorrhoids but until the index finger, or preferably the proctoscope, has revealed no cancer, one should withhold advice. Although constipation of many years' duration is fairly strong evidence of no organic narrowing, yet a barium enema is indicated if for no other reason than to be able to assure the patient that the channel, the main line, is open, even though it is not behaving properly. Especially imperative is the barium enema if the onset of constipation is of recent date. Again, there is the fear of missing an annular carcinoma if the physician too hastily blames change of diet or of water.

The vague dyspepsia may result from a growling gallbladder, from a duodenal ulcer, or from real chronic appendicitis although an acute attack that occurred many years ago may have been forgotten. Even though constipation is present, the inability to tolerate certain foods may not be attributable to the bowel but to these diseases.

In some cases in which the basal metabolic rate is low, elevation of the metabolic rate seems to lessen the constipation. But constipation is such a widespread difficulty that there are not sufficiently accurate data to justify its being considered that it is more prevalent among people whose metabolic rates are low than among others. Usually, elevation of the rate is not enough in itself to correct the difficulty and one must supplement with measures to combat the constipation. The symptoms of fatigue, nervousness, coldness, and so forth are more likely to be the causes of the main complaints, and not the constipation. Although many anal diseases may result in constipation, yet by no means do they always so result. Deep-



seated perirectal infection, anal cryptitis or fissure, or tender, swollen hemorrhoids may produce anal spasm, with semi-voluntary restraint to movement of the bowel in an effort to protect a sore place. This anal disease may all but prevent correction of the constipation until it is treated. Sometimes it may be difficult to demonstrate on the particular day of examination, that there is much anal disease, but to heed the history and to seek the conservative, intelligent treatment recommended by the expert proctologist has been the key to correction of the constipation. To go farther afield and to discuss severance of abnormally large or heavy valves of Houston is more in the field of the proctologist than in mine, although my opinion is that such a procedure is of little or no value.

#### TREATMENT

To the point of annoyance, it is imperative to reiterate the admonition, "Treat the patient and not the constipation." It always smacks of the magician to pull out of the desk drawer a sheet of paper printed months ago and gravely to pass it to the patient who graces the office at the moment. As if the regimen had been carefully planned many months in advance and would be just the thing! Oddly enough, it may reasonably fit the case and the patient may be pleased with the results. It is much more personal, more intelligent, and more practical, however, to consider the patient as an individual. It is no sin to have material on hand from which to choose and then to apply it properly but it is not wise to distribute handbills. A visit with the patient may reveal that the regularity of intestinal movement was first disturbed when attendance at college began, after the first baby arrived, when it was necessary to get to the office or to school after a hurried breakfast, and then to dash to beat the clock, through all walks of life. When the teacher or secretary reports that no toilet room is available on a certain floor, or only one for many, the physician ponders whether he should turn plumber or run an employment agency which promises adequate toilet facilities with each job. With active, healthy children, after once they are housebroken, there is seldom much trouble. A few children seem to begrudge the time to defecate and prefer to squirm rather than hurry when the desire to go to stool is felt. This may result in fecal im-

paction which must first be relieved and then the child must be more carefully watched. At the other end of the road is the elderly person who has slowed up, who takes less exercise than before, whose intake of a none too laxative diet has become decreased, whereas his diet was adequate as he formerly carried on. It is in this elderly group of patients, however, that excess bulk may produce large fecal impactions in the rectum.

While the background antedating the physical phases of life is considered first by the physician, yet first in the patient's mind may be any one of many worries. The physical, and especially the nervous, drain of the social-economic struggle is the fuel which is added to the fire in the anxious mind. The patient does not reason; he merely conjectures and suddenly he is sure that the impossible is true. Perhaps a neighbor or relative recently has been operated on for cancer of the colon, and the mere proof that he has no cancer may so relieve his mind that he no longer is concerned about his constipation, "if that is all it is."

The most difficult phobia is that of "auto-intoxication." I have often longed to sentence the inventor of that term to a hundred years of hard labor, consisting in his being consulted by all his disciples. More or less to the disgrace of physicians we have been too vague, too apparently callous to the complaints of these patients and they have sought sympathy and treatment from colon-slucers and the like. Some people cannot and will not be told and perhaps they might as well be allowed to pursue their own sweet will as to have the physician struggle to convince them. When a patient comes for treatment with his diagnosis established, an all but impossible situation is created at the outset. However, most people are willing to heed an opinion if they have been impressed by the sympathy and thoroughness of the physician. Alvarez approaches the problem with this explanation: "It has been well proved that, even in health, bacteria are constantly going through the intestinal mucosa; most of them are stopped in the neighboring lymph nodes, but some go on through into the liver and perhaps even into the general circulation. This passage of bacteria into the blood stream takes place more easily after purgation and in the presence of diarrhea, when holes are opened up

in the mucous membrane and when most of the bacteria in the bowel are living and virulent. In the presence of constipation the feces are so solid and dry and so lacking in nutriment that most of the bacteria die. Furthermore, it is obvious that little absorption can be expected from solid masses of fecal material. It is helpful to point out to an intelligent patient that few of the poisons that are known to be formed in the bowel can pass unchanged into the portal circulation. Most of them are stopped or chemically altered in the wall of the bowel, and those that get through are likely to be destroyed or changed in the liver or in the capillaries of the lung. Furthermore, any toxin that can get past these several filters must trickle into the general circulation so slowly and in such small doses that physiologic effects cannot be produced. Finally, the physician can assure the patient that there is no reliable evidence to indicate that anyone ever suffered serious injury to the brain or any other part of the body on account of constipation. Anyone who has seen many children and youths with Hirschsprung's disease, with the huge abdomen containing several liters of fecal matter, and yet with a clear skin and no complaint of headache or arthritis or hypertension or epilepsy, must have marveled at the efficiency of the mechanism with which we are endowed to protect us from the absorption of toxic material."

**Food; Diet.**—This has proved the great playground for the unethical food-chemist and dietitian, for the skillful advertiser who is in business to sell his product, and for the sleek individual with a "San Michele" practice. Oddly enough there is often much that is true in even the weirdest food program. It has been difficult for physicians to convince themselves, let alone patients, that not all bowels can be loaded with foreign bulk or that not all people must eat only carefully strained food. Puréed foods, or extra loads of bulk, are proper but must be passed on for each person. One patient may tolerate a fair amount of raw fruits and vegetables; another is more comfortable with most of these articles cooked. Physicians have been willing to recognize that a food may produce a severe gastro-intestinal upset but there is no reason to insist on only raw foods, or only cooked foods, or only puréed foods. Just as the person who recently was an invalid has not yet re-

gained his physical strength, so the patient who has held to a limited slop diet has not the tone for his bowel to accept an overload of roughage.

The ideal of an adequate, well-balanced variety of foods which will meet the need of the body for protein, energy, minerals, and vitamins must be sought. Individual hypersensitivity to one food may not disturb the program but if too large a block of foods is excluded, there must be temporary inclusion of the necessary vitamin concentrates. As the strength and resistance of the patient increase, his ability to tolerate a wider variety of foods is commonly observed. The most frequent omission from the diet of the adult is milk, whether the omission is attributable to actual intolerance, to mere dislike, to fear of gain in weight, or to the belief that milk increases constipation. I see no need of forcing the issue but I do believe that adequate intake of calcium is essential to smooth metabolism and that calcium should be supplied in powders or tablets. The presence of a reasonable amount of fat in the diet tends to make a bulkier, softer stool. Here, again, the problem of obesity may interfere but if it does not enter the situation, generous amounts of cream and butter are advised. Especially helpful is the daily intake of the old, old remedy of three or four tablespoonfuls of olive oil. If the patient has been on a very bland and restricted diet, the sensible, although gradual increase to a normal program of eating probably will increase the sense of abdominal distress and indigestion. If this is mentioned in advance and courage urged to bear with it, there will be less tendency for the patient to become too easily disheartened.

**General Program.**—The following points may serve as guides to treatment:

*Habit.*—In view of civilized customs and the necessity of regard for others, it is usually necessary to have a regular time for the bowel to empty its residue. Neglect of the desire to go to stool often is the first step in the production of constipation and the desire must be regained. The majority of normal people tend to have a movement shortly after arising or after breakfast. But if the day is started with a rush and flurry the bowel is given no chance to function.

*Nervous Tension.*—This great problem of life, and also the

## CONSTIPATION

desire for so-called progress, takes part of its toll in form of the habit of constipation. Under mental and emotive stress, there seems to be an actual clamping down of the bowels. In a few cases, added stress makes for the opposite state, diarrhea. When one's life is, as has been noted in the preceding paragraph, a frantic, hurried, harassed dash from morning perhaps late at night, it is logical that the nervous tension increases, and often constipation supervenes. Although many patients will strive honestly to reestablish the habit of regular movement of the bowel, yet they are in such a constant state of nervous strain that they merely "go through the motions" and cannot relax. Maimonides, a famous Jewish physician of the twelfth century, wrote as follows: "If a man keeps himself busy and tires himself out and then relaxes and keeps his bowels open, he is never sick."

*Exercise and Relaxation.*—Exercise, in the sense of physical activity and relaxation, is often lacking and so the need of maintaining a reasonable muscular tone has a definite place in the regimen. However, exercise alone is not the only thing, as is obvious from the large number of active workers, such as farmers and laborers, who are constipated. Nevertheless, the sedentary worker, who lives chiefly by his mental processes, is more likely to be constipated than his brother who lives by his muscles.

*Food and Fluid.*—The program of eating has been discussed. As to fluid, it is surprising to find how many people, especially women, will drink only two or three glasses of water a day. Explaining that water is absorbed in the large half of the colon to supply the general bodily needs, and that a too dry an intake will result in a drier fecal current moving into the left half of the colon, will encourage the patient to take sufficient fluid: he should take about 2 quarts (2 liters) a day, and more if there is excessive sweating. Other beverages may count toward the 2 quarts. In some instances the thought that discontinuance of excessive drinking of tea helped materially in restoring normal intestinal action to other stimulants, coffee, alcohol, and tobacco, it is doubtful if they directly increase constipation, although their influence through stimulation of the nervous system may be a factor. It has long been noted that the first smoke of the morning may serve to stimulate the desire to go to stool.

*Artificial Aids.*—These include drugs; bulky substances, enemas, and suppositories. These will be treated separately in the following section.

*Evaluation of Mechanical Aids.*—Among the early writings of man, as in the Ebers' Papyrus, for instance, is found advice about drugs for constipation. This work was written about 1500 B. C. and in it are recorded items known fully back to 3500 B. C. Fifteen times mention is made of castor oil; also aloes, oil from seeds, figs and sweet beer are mentioned. Hippocrates devoted attention to the laxatives but urged that they be as mild as possible. The early American Indians knew of the saline waters of mineral springs, and in California they knew of cascara. Francis Bacon wrote, "I commend rather, some diet for certain seasons rather than frequent use of physic except it be grown into a custom. For these diets alter the body more and trouble it less."

A detailed description of laxatives can be found in the books on pharmacology. As to their use, no set rule is sensible. Obviously, there is no need for drugs if the patient obtains results by the previously discussed regimen but if the patient is having a struggle, it seems no great crime to use one of the simpler drugs. How often one is asked, "Now, what is the best laxative?" My reply is that there is no such thing but if our bad habits have established a need of artificial aid, the patient should use that which accomplishes the result with the least possible general disturbance. I have preferred simple magnesia, fluid extract of cascara, or senna. Rather than whip the bowel with a single maximal dose, division of that amount into three portions and taking one of the portions after each meal, seems to give the extra push, as well as making it easier gradually to decrease the need for the drug. So often it has seemed more sensible to supplement the general regimen with divided, small doses (10 to 30 drops) of cascara after each meal, than to make a willing but miserable patient fight without help, probably after an enema-physic diet struggle of months or years. Especially for older people the little chemical irritant seems to be practical. Dr. W. J. Mayo said to a patient, "I can't see that taking a little physic is going to do you any more, if as much, harm as filling your stomach and bowel with a lot of rabbit food." When drugs are prescribed, it is with the

idea that they are merely crutches to help until the good habit replaces the bad one. It should be stressed that laxatives are no more a cure for constipation than are sedatives cures for "nerves" but both are valuable if intelligently used.

Belladonna has had first place for many years to relieve spasm. The actual evidence on which its use is based is so meager that I see no need to use it; the chances of intolerance to the drug developing are probably greater than the chances of any actual benefit.

Next in mechanical aids arises the question of enemas and how the great and near-great have flung that question back and forth. From the time of the bladder with its horn or bone tip to the time of the stupendous, expensive colon-sluicing machines, there has waged much clamor. As with laxatives, enemas are merely artificial, transitory aids in the correction of a bad habit. They are not cures, irrespective of the solution used. Nor is it likely more heinous to use an enema than it is to use a simple laxative. But again, emphasis must be laid on merely tiding over until the real factors can be more fully corrected. It seems futile to debate laxative versus enema; both are theoretically wrong but practically, whichever causes the least annoyance and is the simpler for the patient who must use a crutch it seems logical to me to use it. Wise Paulus Aegineta, in about the seventh century, wrote, "Clysters must not be repeated constantly lest nature, becoming accustomed to these things, should forget to perform the evacuation spontaneously." Certainly my opinion is not original and I am not sure whom Aegineta may have quoted. As to what kind of enema to use, I suggest warm physiologic saline solution (1 teaspoonful of salt to the pint). This is the least irritating solution. Allowing a pint to run in slowly, repeating if necessary, usually will prove effective.

Oils have been in vogue for centuries. The ancients used oil from various seeds or fruits which they prescribed either for oral administration or, if the stools were dry and hard, for administration by enema. Our era has added mineral oil which, of course, is undigested and merely slides through as a lubricant. In many cases, just this much artificial aid, a "swig" of oil at bedtime, gives excellent results. In other cases, it seems to cause indigestion or may trickle on through the bowel

without mixing with the feces. Emulsifying the oil with agar tends to overcome this objection but these products are expensive. Although olive oil is largely digested and absorbed, yet its oral administration long has been helpful; barring obesity or intolerance, I prefer a trial of it rather than of mineral oil.

Of recent, well-advertised origin is yeast, and there is no doubt that ingestion of yeast may give the extra push. In my experience, it fails oftener than it succeeds. Certainly it is harmless enough to try. There is no question of the changes that occur in the digestive tube when the diet is deficient. Some people may have coasted along on just a subthreshold margin which the yeast may correct. Bread dough, mixed with milk and honey, was recommended by the early Egyptians; maybe the bread dough is the first suggestion of the use of yeast; again we are 4,000 or 5,000 years behind!

Buttermilk and acidophilus milk have had their advocates in great waves, both scientists and advertisers. As to the latter, charity and not caustic comment is due; with 70 to 80 per cent of the population more or less constipated, there is a big group for advertisers to reach. I am convinced that many people have felt better and that their bowels have acted more regularly if they drank one or another of these milks. Whether they merely increase the fluid and bulk, or whether there is some bacterial action, I do not know. The fact that a good growth of *Bacillus acidophilus* in the bowel can be obtained by ingesting an ounce of milk sugar, just as can be obtained by drinking a quart of the milk, without seeming to improve constipation, has led me to doubt the great value of the bacterial change. Also, discontinuance of ingestion of the milk or milk sugar results in prompt return to the former level of the *Bacillus acidophilus* in the stool. Surely there is no objection to *Bacillus acidophilus* and if it helps, fine!

What about bran, various seeds, vegetable mucins, agar, and so forth? Most physicians now agree that people have gone far beyond the bounds of common sense in the manner in which they have poured foreign, insoluble stuff into the digestive tube. Granted, indeed, many people have been able to tolerate, and their intestines have functioned better with, this wadding, but for one of them there must be five, probably fifty, to whose



distress it merely has added. Again to quote Dr. W. J. Mayo: "It is bad enough to stuff on rabbit food without packing your bowel full of sawdust." Some physicians feel that it is unwise for whole wheat cereals and breads to be routinely included in the diet. Again, if any of these things help there is no argument but I do not recommend them as a rule. Rectal masses, the size of a large grapefruit, may occur from use of bran or vegetable mucins, particularly if people are elderly. If these substances are used at all, they should be taken in only small doses, and later it should be ascertained that the stuff is not packing in the rectum, even though the patient may be having daily movement of the bowel. In my experience, plain granular agar has been the least objectionable form in which to supply artificial bulk and if bulk must be added by means of this substance, to use it in doses of 1 to 3 teaspoonfuls with each meal.

Sometimes the physician is confronted by the desperate patient who actually begs for an operation, omitting, of course, correction of an anorectal pathologic condition. Many physicians have seen patients who have undergone right hemicolectomy, fixation of the mobile cecum, "tacking up" of the fallen transverse colon, or even ileosigmoidostomy, and still have constipation. I am opposed to any of these procedures to correct constipation; they occasionally have succeeded but in the majority of cases they have failed and in what a state those patients are! Possibly something may be worked out in the field of neurosurgery, although the results in cases of megacolon are not always successful. As yet, this must remain in the field of the experimenter.

**Constipation in Disease.**—Constipation is often a troublesome symptom in many diseases. In 200 A. D. a Chinese physician urged that only enemas be employed for the constipation of severe intestinal fevers (typhoid fever), no doubt from knowledge of patients dying after taking a purgative.

In pneumonia or in any illness which forces the patient to his bed, restriction of food, lack of activity, and possibly of greater importance the effect of toxemia on the nerve centers, create the difficult symptom of constipation. The use of various enemas, the type of which will vary with each locality, may suffice. Simple glycerin suppositories occasionally are effec-

tive. Hot abdominal stupes, if not too heavy, or the electric pad have seemed helpful, possibly more because of psychologic than the actual physical effect. Recently I have been impressed by the use of short wave diathermy over the abdomen; this may result in emptying of the bowel. It should be needless to caution against laxatives when one is not sure that there is no actual intestinal obstruction. Present records on appendicitis certainly show that the advice not to give purgatives to patients who have abdominal pain still will bear loud repetition. Hypodermic administration of pituitrin, acetylcholine, eserine, and so forth should be employed only after failure of other methods. Use of these drugs is not without danger and much caution and judgment must be exercised in their employment.

### CONCLUSION

Constipation is age-old and has been known of from the dawn of civilization. It is a habit and an expression of disordered living, physical or emotional; and usually both. It should be approached and treated as an error in living and not as a disease. The several thousand years' accumulation of advice, which is now greatly enhanced by present methods of communication, have done more to confuse than to help. Many present ideas, "notions," have their roots in antiquity and this knowledge should broaden our common sense approach to the problem. As with any other condition or with any disease, the patient should be studied and treated as an individual and not as just another case. And this is difficult to do!

## THE TREATMENT OF DIARRHEA

J. ARNOLD BARGEN

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ONE of the most common, and often very distressing, symptoms of human disease and behavior is diarrhea. To consider its management under this broad title presumes delving into all manner of bodily dysfunctions. In general, it can be said that there are those conditions in which the symptom diarrhea is associated with disturbances outside of the intestine and those in which diarrhea is the result of disease of the intestine. Persistent or recurrent diarrhea may or may not be of serious moment, but its cause should be searched for in each instance with the greatest care. A most thorough investigation of each case of diarrhea is necessary to establish it as a symptom of a general bodily disorder or of local disease. Obviously, a thorough search of the digestive tract is in order in each case. In the main, it can be said that when diarrhea is the result of disturbances outside of the intestine the treatment is largely symptomatic or at least directed to the alleviation of the condition in which diarrhea is only one of the symptoms. This observation simplifies the story of management considerably. The conditions which may cause diarrhea are listed in the Tabulation. It is apparent that the diarrheas associated with conditions outside of the intestine are the result of reflex disturbances of intestinal function. It also follows that all the functional disorders, whether local or systemic, may be grouped together to simplify the study of their management.

On the other hand, all organic intestinal disorders must be considered individually for adequate therapeusis. It has been suggested that a real diagnosis cannot be made in even half of the cases of diarrhea. One must not confuse, however, the cause of diarrhea with the mechanism of its production. Even though the latter might not be explained in a given functional disturbance, the diagnosis may still be correct. The important

## TABULATION

## CONDITIONS ASSOCIATED WITH DIARRHEA

1. Systemic disturbances:
  - (a) Nervous diarrhea.
  - (b) Allergic diarrhea.
  - (c) Food poisoning.
  - (d) Trichinosis.
2. Metabolic disorders:
  - (a) Hyperthyroidism.
  - (b) Uremia.
3. Functional gastro-intestinal disorders:
  - (a) Irritable colon, unstable colon or "mucous colitis."
  - (b) Gastrogenic diarrhea.
  - (c) Foreign bodies.
4. Organic intestinal disorders:
  - (a) Neoplastic:
    1. Polyposis.
    2. Carcinoma.
    3. Other tumors.
  - (b) Non-neoplastic:
    1. Ulcerative colitis:
      - (a) Streptococcic.
      - (b) Tuberculous.
      - (c) Parasitic.
      - (d) Infectious diarrhea of undetermined etiology.
    2. Infectious dysentery:
      - (a) Bacillary dysentery.
      - (b) Typhoid fever.
    3. Granulomatous lesions:
      - (a) Tuberculomas.
      - (b) Amebic granulomas.
      - (c) Infectious granulomas (nonspecific).
    4. Regional enteritis, colitis, and enterocolitis.
    5. Deficiency diseases:
      - (a) Pellagra.
      - (b) Sprue

fact remains that a thorough systemic examination of the intestine must be made in order to determine the cause of any diarrhea. The cause of diarrhea should never be considered either unknown or functional until disease of the intestine has been excluded.

The most important diagnostic method in cases of diarrhea is the taking of detailed histories. However, to rely on the history alone will result in many regrettable errors of omission.

Many physicians will recall cases of irritable colon in which treatment for colitis was employed for months or, what is more serious, they may recall cases of carcinoma in which the mistaken diagnosis of colitis was adhered to until chance of cure had faded. Therefore, while a history is an indispensable and most important guide to the diagnosis, no other group of conditions which produces similar symptoms lends itself so well to further routine study as do conditions associated with diarrhea. A well-regulated set of objective investigations will lead to the correct diagnosis in nearly all cases of diarrhea.

### SYMPTOMS

Although some authors make an attempt to differentiate stools of so-called dysentery and diarrhea, for practical purposes they may be considered under the same general heading. The distinction between dysentery and diarrhea is more apparent than real, and dysenteric stools may alternate with diarrheal stools in a single case. Of greatest value is the nature, type, and severity of the diarrhea in a given case. Whether a patient has twenty loose, watery stools, or three or four mucopurulent rectal discharges is of great diagnostic importance. The rectal discharge of bloody, purulent material without much, if any, solid material is suggestive of chronic ulcerative colitis. On the other hand, the stools of patients who are suffering from intestinal tuberculosis, amebiasis, bacillary dysentery, food poisoning and so forth are so variable that they only occasionally contain gross positive diagnostic evidence.

The presence of blood in the stool is always indicative of some type of organic disease. The manner in which blood is ejected from the rectum may offer suggestions of the nature of the lesion. If passed separately, just before, or surrounding the stool, it is more than likely the result of local anal disease. If intimately mixed with mushy stools or purulent discharges, it is the result of disease above the anus, probably in the rectum or above. The freshness of the blood is in direct ratio to the proximity of the disease to the distal segments of the large intestine. It is well to consider all rectal bleeding as attributable to carcinoma until proof to the contrary is available.

The presence or absence of mucus in the stool has no diagnostic significance. Mucus is the normal colonic secretion.

The quantity of pus in the stools or rectal discharges has great significance.

Patients who have diarrhea may or may not have pain. The pain may be of two principal types. One type, which is spoken of as tormen, consists of griping, colicky distress in the abdomen and is associated with lesions of the right half of the colon. The other type, which is known as tenesmus, occurs with painful, spasmodic contractions, is accompanied by a feeling of incomplete evacuation and straining, and is associated with lesions in the distal segments of the large intestine.

Emaciation, rapid loss of weight, and anemia are frequently associated with diarrhea.

#### GENERAL PHYSICAL EXAMINATION

General inspection of the patient is important. The facies is often suggestive of the type of disease. Pallor and anxiety occur with severe organic disease or, on the other hand, full robust features may be noted in cases of functional disorder. Examination of the thorax may elicit the findings of tuberculosis. The scaphoid abdomen may suggest tuberculosis or chronic ulcerative colitis. The cord-like feeling imparted by the colon, if on the left side, may be suggestive of chronic ulcerative colitis, or if on the right side, it may be suggestive of other inflammatory disease. Finally, the most important part of the physical examination is careful, digital examination of the rectum. The wall of the rectum in all functional disorders is soft and pliable, and the mucosa is smooth and velvety. The wall of the rectum in amebiasis and tuberculosis may also be soft and pliable but if lesions have involved the rectum, irregular depressions will be found in the mucosa. The wall of the rectum in chronic ulcerative colitis will be stiff, and thick; the lumen will be narrowed, and the mucosa will appear roughly granular. Polyps in the rectum are readily palpable and carcinoma imparts a characteristic feeling to the finger.

#### ORDER OF SPECIAL EXAMINATIONS

There is probably no other symptom-complex in which the order of special examinations is as important as it is in conditions associated with diarrhea.

**Examination of Stools and Rectal Discharges.**—Stools and rectal discharges should be examined first and repeatedly until the examiner is thoroughly satisfied about the presence of suspected bacteria and parasites. Gross inspection of the stools is important. In some stages of chronic ulcerative colitis the characteristic sanguinopurulent rectal discharges alone allow a diagnosis to be made. Microscopically, the large amount of pus is striking. Charcot-Leyden crystals are, almost without exception, abundant. Streptococcal forms of bacteria predominate.

A typical stool of bacillary dysentery contains a relatively small amount of pus, and a great deal of mucus. It is usually liquid; it even may be "ricewater-like" and may contain blood. Although this condition is relatively rare in the northern half of this continent, its presence should be considered in every case of severe dysentery. Then, too, a few men have described chronic ulcerative colitis as a phase of bacillary dysentery. Hence, one should constantly be on the alert for the presence of the latter condition. Microscopic examination of the feces of patients who have bacillary dysentery will reveal many large phagocytic cells, which may easily be confused with amebæ for these cells also may contain erythrocytes. Staining will readily distinguish these cells from amebæ. An important point regarding the cultures of stools of patients who have bacillary dysentery concerns the fact that the stools should be examined immediately after they have been passed. Colonel Craig said: "The patient should be removed from the bedpan in order to inoculate media, preferably at the bedside." The reason for this great haste in examining stools is the fact that it has been demonstrated that the organisms undergo autolysis on standing. Various types of *Shigella paradysenteriæ* (dysentery bacilli) have been demonstrated in the Northwest; among them many mention the types of Flexner, of His and Russell, and of Sonne. *Shigella dysenteriæ* has not been encountered in this part of the country.

Although typhoid fever probably should not be considered among disorders associated with diarrhea, it has been estimated that more or less severe diarrhea may occur at times with passage of blood in a third of the cases, during the first half of the illness. Hence, this disease should be kept in mind in a study

of any severe type of diarrhea. The *Eberthella typhosa* can be isolated from the stool or urine in about half of the cases during the first two weeks of the illness, and even more frequently during the third week. Inasmuch as there is nothing characteristic about the stools in the cases of typhoid fever in which diarrhea is present, the importance of suspecting this disease in cases of diarrhea becomes apparent.

Another disease in which the study of stools is the most important diagnostic procedure is amebic dysentery. In acute amebic dysentery, the typical stool will contain dark brown shreds of mucus, and the whole stool, which is usually small in volume, will be a dark brick-red color. Flecks of bloody mucus may be mixed with the stool. These flecks of mucus often contain large numbers of amebæ. It is best to examine liquid stools in searching for amebæ. The finding of the *Endamœba histolytica* in the stools of patients who have diarrhea or dysentery is significant, and although the host may be only a carrier of this organism, its presence goes far in establishing a diagnosis.

In intestinal tuberculosis the gross appearance of the stools gives but little help. Gross blood rarely is present. The stools may be liquid or soft, and even may be formed. One should be suspicious of this lesion in a case of colonic ulceration in which the presence of pulmonary tuberculosis has been demonstrated.

There is another type of diarrhea which occurs in association with food poisoning. An intestinal disturbance often has been blamed on something the patient ate. Such a diagnosis has often been found competent, but more definite information is at present available and unless the condition promptly subsides, examination of the stools should be undertaken. The gastro-enteritis associated with food poisoning is apparently caused by various organisms, of which the staphylococci are the most prominent.

There is no peculiar characteristic about the stool of a patient who has polyposis, except that it will contain blood. The same can be said about the stool of a patient who has carcinoma of the colon.

**Proctoscopic Examination.**—The proctoscopic examination is the second most important test to determine the cause



of a diarrhea. It is well to wash out the rectum with warm enemas before performing the proctoscopic examination. Examination of the stools should be performed before the proctoscopic examination. Many organic lesions of the colon can be positively diagnosed by visualization through the proctoscope or sigmoidoscope. Thus, the pictures of uncomplicated chronic ulcerative colitis, tuberculosis, and amebiasis are characteristic. Proctoscopic examination of the rectums of patients who have polyps or carcinoma offers the added advantage of allowing removal of specimens. Frequently, the diagnosis of diverticulitis can be made through the proctoscope by visualization of the upper rectal sacculum and spasm. Proctoscopic examination is of great importance in functional colonic disorders, because it discloses the fact that the lining of the bowel is normal.

**Roentgenologic Examination.**—The roentgenologic examination should always be the final one of the series of examinations. The most important aid in a satisfactory roentgenologic examination is an empty colon. Consequently, the administration of some purgative, followed by intestinal irrigation, is essential. At the Clinic we follow a program something like the following one: The patient receives a dose of castor oil a day previous to the examination. No food is given for eighteen hours before the examination. On the morning of the examination, enemas are given until they return clear. The best results are obtained by retrograde filling of the colon by the barium enema, followed by evacuation of the colon and then by the injection of air under roentgenoscopic control. With the barium enema, gross filling defects will be detected and on the roentgenogram, which is made after evacuation, the mucosal pattern and any lesion disturbing it can be seen. Following the insufflation with air, small intrinsic lesions can be detected. Each one of the chronic organic intestinal lesions will present characteristic roentgenologic deformities in the colon. To detect lesions in the small intestine, it may be wise to observe the barium meal as it passes through the small intestine. If this becomes necessary, it should always follow the examination with the barium enema and should not precede it.

**Other Procedures.**—Other procedures may be advisable in the study of any given case of diarrhea. These may include

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**Other Procedures.**—Other procedures may be advisable in the study of any given case of diarrhea. These may include

the analysis of the gastric contents, investigation of allergy, determination of the basal metabolic rate, and tests for elimination. Invaluable information will be obtained by blood cultures in typhoid fever or by agglutination tests, such as the Widal test in typhoid fever or similar tests in bacillary dysentery. Important information at times can be gained by the study of blood smears. In the aggregate, however, these tests will give information in a relatively small number of cases.

#### TREATMENT

**Systemic Disturbances.**—When it has been definitely established that a diarrhea is the result of a disturbance of this type, treatment may often be very difficult. The most important factor in a well-regulated program of management in these cases has to do with convincing the patient that the diarrhea is of this nature. It may not be easy to establish in the mind of an individual that his nervous irritability is causing a diarrhea. For this reason, the objective tests which have been described become an important part of the treatment. When the nature of the systemic disturbance has once been established, the treatment of the diarrhea itself becomes a secondary problem. The patient may have to avoid those things which upset his nervous system. He may have to avoid certain foods which are followed by intestinal disturbances. Of course, when diarrhea is the result of such things as food poisoning and trichinosis, the specific treatment of these is in order. When it is caused by exophthalmic goiter the adequate treatment of the hyperthyroid state will result in the control of the diarrhea. In my experience, diarrhea only occurs in the late stages of uremia, when treatment of the uremia state may not be possible. In any event, however, the treatment should be directed to the renal condition rather than to the intestine. The same things may be said about the control of the functional gastrointestinal disturbances. The so-called irritable colon, or unstable colon, which also has been described by some writers as "mucous colitis," is a condition in which the intestine plays only a small rôle in the production of the diarrhea. The colon is only one of the organs whose function is deranged. While relief of the diarrhea may be advisable, the major part of the treatment should consist of the control of the general bodily

disturbance. Frequently, frank talks with the patient, in which every effort is made to dispel acquired fears and to replace them by exact information as to the nature of the difficulty, are important. It must be explained that sensitiveness of the colon is a characteristic part of that individual. Analysis of the patient's emotional and mental state becomes necessary. However, even when complete understanding and agreement between patient and physician have been established, the treatment is not ended. The patient must then be taught how to overcome and to live with a disability which, although not serious, is exceedingly troublesome. A detailed regimen should be outlined; this should include diet, physiotherapy, administration of drugs, and many other details from which the patient should not be allowed to deviate. No fixed regimen is possible for all of these patients. The program must be individual and will entail patience by the patient and physician alike.

**Organic Intestinal Disorders.**—The treatment of each of these conditions is essentially individual. The treatment for neoplastic disease has been well established and can be summed up by saying that it is essentially surgical and radiologic. The important consideration from the clinician's standpoint is accurate diagnosis.

**Ulcerative Colitis.**—In cases of ulcerative colitis the treatment for each type of this disease has been well established. In the condition known as chronic ulcerative colitis of the streptococcic type, the treatment is chiefly medical. The present management includes the following details: (1) rest and restful recreation, (2) a careful dietary program, (3) administration of serums and vaccine, (4) removal of foci of infection, (5) transfusion of blood, (6) supportive measures, (7) careful nursing, (8) physiotherapy, including hydrotherapy and occupation therapy, (9) administration of drugs, and (10) local treatments.

Chronic ulcerative colitis should be looked on much as is tuberculosis, and a well-regulated, graduated program of rest, which at first consists of rest in bed, then graded activity, and finally mild physical recreation, is in order.

Many patients who have had this disease have, in the course of time, omitted one food and then another from their diet so that ultimately their diet has become very limited. It is well

then to return them by easy stages to a generous, high-caloric, high-protein type of diet, beginning with easily assimilated, palatable, nonirritating foods and increasing the diet day by day as rapidly as their condition will tolerate. Not infrequently, solutions of dextrose administered intravenously or the subcutaneous administration of a physiologic solution of sodium chloride are indicated to restore an adequate fluid balance.

The serum prepared by immunizing horses against the diplostreptococcus of colitis may be administered intramuscularly or it may be administered intravenously in cases in which the condition is severe. Results with the use of this serum are most gratifying. The anticolon bacillus serum recently prepared by Schwartzman bids fair to have value. The reactions from anti-dysentery bacillus serum are frequently so severe that its use is indicated only in cases in which the condition is resistant to treatment. Its value as anything more than a nonspecific foreign substance is problematical. Vaccines prepared from the diplostreptococcus which has been isolated from the rectal ulcers should be administered subcutaneously in cases in which the infection is less severe or when active and severe symptoms have subsided.

Distant foci of infection, particularly about the mouth, such as infected tonsils and abscessed teeth, should be removed.

Blood transfusions are of value in two phases of the disease: (1) when the individual has had a long siege of fever and sepsis, and (2) when he is anemic. A series of transfusions of small amounts of blood, that is, about 250 c.c. each, given every four or five days, for four or five weeks, have much greater value than one or two transfusions of larger amounts.

Osler has aptly said: "Disease above the diaphragm makes for optimism and that below the diaphragm for pessimism." Hence, in this disease, any measures which will produce physical stimulation and divert the patient's attention from his condition are in order. For this reason, mild forms of occupational therapy are of great value.

Many drugs have been advocated in the treatment of chronic ulcerative colitis. No single one has helped more than a few individuals. Sedatives, particularly codeine and other forms of opium, are decidedly indicated in severe forms of

the disease. Tincture of iodine, given by mouth, is of value in selected cases. Arsenic, in the form of stovarsol, treparsol (the methenamine derivative of meta-amino-para-oxyphenyl-arsenic acid), or carbarstone, is dangerous when used in the treatment of chronic ulcerative colitis. It frequently has seemed to be the basis of severe exacerbations. Its only indication is as a tonic and it should be administered in very small amounts after the patient has ceased passing blood. A warning should also be expressed about the use of mercury in such forms as mercurochrome.

Local treatments are indicated only when there is much anal discomfort, as from fissures and fistulas, or when the lesions are confined to the most distal segments of the large intestine. Chronic ulcerative colitis is not a disease of the mucosa but of the intestinal wall, and hence colonic irrigations not only fall entirely short of the purpose for which they are intended but often cause irreparable irritation.

From these remarks, it becomes obvious that a well-regulated program of activities is necessary for adequate treatment of patients who have chronic ulcerative colitis.

**Parasitic Disease.**—Although, in various parts of the globe, many parasites inhabit the human intestine, for practical purposes a consideration of the treatment of amebiasis will suffice. Chemotherapy plays a very important rôle in the treatment of amebic dysentery. The purpose of therapy in these cases is twofold: (1) to eradicate the parasites in the walls of the intestine and in other distant foci, and (2) to promote healing of the lesions they have produced.

The following combinations of drugs have been found to produce these results in a very satisfactory manner. In the average case, emetine hydrochloride  $\frac{2}{3}$  grain (0.043 gm.) is administered hypodermically, twice a day, until 4 grains (0.24 gm.) have been given. In cases in which the disease is more acute 1 grain (0.065 gm.) of emetin hydrochloride, is administered twice a day, until a total of 6 grains (0.4 gm.) have been given. At the same time, tablets of treparsol, each of which contains 0.25 gm. of the drug, are administered. One tablet is chewed before each of twelve successive meals (three tablets a day), the course of treatment taking four days. A rest for a week follows, and the same course of treatment is

repeated. Two courses of treatment with emetine are usually sufficient, and it is seldom safe to give more. Three courses of treatment with treparsol are usually required. Between the second and third courses of treatment with treparsol, and after the third course, one of the compounds of iodine, such as chiniofon may be given. This is prescribed in the form of tablets which contain 0.25 gm. of the drug.

Diet should be generous but bland; it should be graded more bland or less bland, according to the severity of the disease.

After completion of the course of treatment, the stools should be examined by a competent parasitologist, and the examination should be repeated again in several months.

**Tuberculosis of the Intestine.**—The common type of intestinal tuberculosis secondary to disease of the lungs resembles amebiasis in its involvement of the intestine. No specific treatment for it is as yet available, hence the differential diagnosis of these two conditions is of utmost importance. Rest in bed and heliotherapy constitute the keynote of treatment. The object must be to take as much of the burden off the inflamed and handicapped bowel as is possible. The diet should be somewhat similar to that used in chronic ulcerative colitis; it should be smooth, relatively low in residue and high in calories. Attempts at specific treatment have included the injection of oxygen into the peritoneal cavity, roentgen therapy over the abdomen, injection of oxygen into the abdomen, and even opening and closing the abdomen surgically. Among the drugs which have found favor in the treatment of this condition are calcium, arsenic, and mercury. Many other drugs have been employed but the important thing to remember is that intestinal rest is of paramount importance. The prognosis of tuberculous enterocolitis is unfavorable and the condition usually is a terminal process.

**Infectious Dysentery.**—The management of any patient who has acute dysentery should be the same as the management of a patient who has one of the transmissible forms of dysentery, such as typhoid fever or bacillary dysentery. Precautions that accompany isolation should be applied. The diagnosis will usually be settled by blood cultures or agglutination tests, such as the Widal test for typhoid fever or similar tests for bacillary



dysentery. Once the diagnosis has been settled, the usual supportive measures described for severe chronic ulcerative colitis are in order. Of utmost importance in the management of the patients is their nursing care. Various types of diets have been suggested; those high in carbohydrates and low in residue have found greatest favor. Specific treatment, such as administration of a serum or a bacteriophage and the later administration of vaccines, should be employed in these cases.

**Granulomatous Lesions.**—At this time the accepted treatment of tuberculomas and infectious granulomas (nonspecific) is surgical. Some form of short-circuiting operation, usually followed by resection, is in order. Here again, however, it is of utmost importance to distinguish these lesions from the so-called amebic granulomas for in the latter condition specific anti-amebic treatment will usually suffice unless paracolonial infiltration has become so great that obstructive features predominate.

**Regional Enteritis.**—This condition which has been considered an entity only in recent years, is an infectious disorder of localized segments of the intestine. The best treatment is still debatable but most men with considerable experience in handling the condition are advising surgical excision of the affected segment or segments, as "skip areas" often are present.

**Deficiency Diseases.**—More time and space than are available for this entire paper could be adequately devoted to a consideration of these diseases. For practical purposes, pellagra and sprue are probably the principal ones requiring consideration. It is important to determine, if possible, just what is lacking in any given case of deficiency and then treat the patient by supplying the food, mineral or other substance which is the cause of the deficiency. In a case of active pellagra, a high calorie and high vitamin diet is probably the most important single measure of safety. Supplying all the necessary food elements, and at times supplying more than adequate quantities, may be enough to control the pellagra. At the onset an excess of vitamin B should be given by using B concentrates. In a case of sprue, the factor of anemia is frequently one which must be dealt with very drastically, hence the administration of many of the drugs used in the treatment of anemia may be indicated. Liver extract, preferably administered hypoder-

mically, is of value in the treatment of sprue. Dilute hydrochloric acid, administered by mouth, may be advisable as substitution therapy. A diet rich in carbohydrates, high in proteins and relatively low in fats has been most efficacious. Frequently even carbohydrates are poorly tolerated at the onset and must be added slowly. Deficiencies may be secondary to any other bodily state that may be associated with diarrhea. These are usually best managed by control of the basic pathologic changes.

#### SUMMARY

I have attempted to offer a few practical suggestions for the control of some of the common diarrheas. A perusal of this paper will promptly bring to mind other conditions associated with diarrhea. Space will not allow individual consideration of all these conditions. Most of the other diarrheas, at least those found in the North Temperate Zone will represent symptoms of other bodily disturbances which at times are distinct from the intestine. Their management is usually individual and symptomatic.

## "SPASTIC COLITIS"; FUNCTIONAL DISORDERS OF THE COLON AFFECTING YOUNG AND MIDDLE-AGED INDIVIDUALS

E. G. WAKEFIELD

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THE functional disorders of the colon, often termed "spastic colitis," "colitis," "constipation," or "irritable colon," are manifested by irregularity of evacuations and by apparent alternation in the absorptive and secretory functions of the colon. These terms are usually applied to conditions which are considered as separate clinical syndromes. It is our opinion at the Clinic that this is not the best conception of functional disorders of the colon. These separate syndromes are phases of the same clinical disorder. Since this is true, the clinical symptoms will be described first in order to define the condition clearly.

### SYMPTOMS AND PHYSICAL SIGNS

The irregularity of the evacuations may vary from one bowel movement a week to ten or twelve or more in twenty-four hours. When there are infrequent evacuations, the feces often are like pellets and are tangled in masses of slime. Between irregular defecations there may be passages of slime or mucus, which may be formed or cast, the so-called "mucous casts." Periods of increased evacuations are characterized by an apparent increase in the volume of watery feces which may also contain slime or mucus. In any one case there may be periods in which there are all gradations between the extreme degrees of constipation and diarrhea. Some patients constantly have varying degrees of "loose stools" while others always are extremely constipated. Characteristically, in cases in which the stools are loose, the patients have their bowel movements after meals, especially after breakfast. It is very rare that

the nocturnal sleep is disturbed once sound sleep has been obtained. Abdominal discomforts to the degree of real pain may be present. The pain is usually low in the abdomen and most frequently along the course of the colon and on the left side; however, no part of the abdomen is exempt. The pain may be associated with bowel movements. The severity of these disorders of the colon may be measured by observing the frequency and degree of the symptoms and the ease with which the colon may be provoked to change its habits so widely. A patient who has had a long-standing disorder of the colon which has not been associated with the passage of feces containing blood, with remission of symptoms, and with loss of weight will usually be found to have a functional disorder of the colon. The disorder which has been termed "irritable colon" or "spastic colitis" is often characterized by paroxysmal attacks of abdominal pain which are associated with fatigue that follows either emotional disturbances or physical strain.

The clinical history of a functional disorder of the colon may reveal the presence of every known symptom which can arise from organic disease of the colon. In eliciting the history in a case in which the symptoms are referable to the intestines, there are certain points which should be clearly elucidated. Organic diseases of the colon, as a rule, are characterized by fever, loss of weight, blood in the feces, and symptoms which awake the patient after he has gone to sleep at night. These symptoms are usually absent in functional disorders. Loss of weight, if present in cases of functional disorder of the colon, can usually be accounted for by sitophobia, or are the result of a diet which has been prescribed by a "diet specialist." The history of a change in bowel habits has been considered almost an infallible sign of organic disease. This change may vary from constipation to diarrhea or there may be alternating constipation and diarrhea. A change in bowel habits would also include the opinion of the patient that the action of the intestine was not right or had changed in some indescribable way. If one could accurately elucidate this point in the history, its value in the differential diagnosis of organic disease would be established; however, in reality, the so-called alternating diarrhea and constipation can usually be definitely attributed to the taking of laxatives. If the use of laxatives could be avoided

in organic disorders of the intestine, the trend would be definitely toward either a constipation or a diarrhea. In other words, the colon which is organically diseased tends to maintain a stability of function, whereas, in the presence of a functional disorder the colon tends to lose this stability and, as has been stated, may be easily provoked to change its habits widely. The stability of the action of the colon is best illustrated by pointing out that at least two-thirds of those who have carcinoma of the colon are not disturbed by any degree of irregularity of intestinal action, and they do not seek relief until there is abdominal pain or discomfort, sudden onset of obstruction, or rectal bleeding which causes them to become alarmed about the extent of the loss of blood and the weakness.

The general physical examination of a patient who has a functional disorder of the colon does not reveal anything that is characteristic. Many normal persons have a palpable cecum, a palpable ascending colon, or a palpable sigmoid flexure. The loss of weight, hyperactive reflexes and subjective abdominal tenderness are of no real diagnostic value. If the abdomen is tender, similar tenderness often can be elicited by pressure over various parts of the body, especially over the distal portions of the tibiae. There is a general increased susceptibility to pain. There may be a pathologic tendency toward fabrication, evasiveness, arrogance, irritability and fixed ideas concerning the illness but this is not peculiar to disease of the colon. Direct visualization of the rectum, rectosigmoid and sigmoid flexure with the sigmoidoscope will reveal a normal mucous membrane. Roentgenographic examination of the colon in these disorders might be of specific diagnostic value if a properly controlled series of normal persons were available for comparison. In the roentgenologic study of such a controlled series of normal persons, due consideration would have to be given to the limits of the varying responses of the colon to the preparation for the examination and to the effects of the presence of the mass and volume of the opaque material and feces in the intestine. At the present time the great value of roentgenologic examination of the colon in cases of functional disorders of the colon is the ruling out of deforming lesions. The roentgenologist is familiar with the fact that roentgenologic examination may reveal great coils of the intestines which are kinked and

tethered by adhesions and knows that acute bends of the colon may be present without producing clinical symptoms. Furthermore, the roentgenologist is fully aware of the fact that whether the colon is on the right or left side, or whether its flexures are under the costal margins or in the pelvis, its functions may still be normally performed.

### ETIOLOGY

The etiologic theories of functional disorders of the colon comprise an interesting chapter of medical history. These disorders have long been the bane of many human lives. It is fairly safe to say that the human race has suffered from these disorders since the dawn of civilization. The ancient Egyptians purged themselves three days in succession each month, thus seeking to preserve health with emetics and clysters, for they supposed that all diseases were the results of accumulation of refuse in the intestines. Europeans during the Middle Ages resorted to the use of the horoscope to determine the proper time for emesis and purgation, while the American Indians and ancient Babylonians had fixed periods for ritual emesis and catharsis. It has been observed that the feces contained in the rectum of a mummy found under a bluff in the plateau region of the Ozark Mountains was in the form of pellets, in other words, a constipated stool. This mummy lived 2,000 or more years ago. It was not until the eighteenth century, when John Howship recorded under the heading of "Practical remarks on the discrimination and successful treatment of spasmodic stricture in the colon considered as an occasional cause of habitual confinement of the bowels," that there was any evidence of a clearly stated conception of the etiology of functional disorders of the intestines. Howship considered these illnesses to be the result of a deficient freedom of relaxation in some part of the intestinal canal. However, his reports contained at least one case which was most likely an example of an organic disease. In this case the condition was probably an intussusception of the small intestine. This report of Howship was mainly valuable, as has been stated, for the conception that it contained, a conception which seems to have been quickly lost or completely forgotten because medical writers continued to be enamoured by the "beneficial effects of purg-

ing." About the only evidence that a failure of relaxation of the intestine was a part of the disease is indicated in the term "spastic colitis," which is probably a hybrid linking the conception of Howship with the more modern science of bacteriology.

On the discovery that the human colon was a culture tube for very large numbers of bacteria, many ill-advised conclusions were formulated, which suggested the theory that all the diseases of the colon and the lower part of the intestine were caused by microorganisms, and the term "colitis" consequently was applied to any obscure disorder of the colon. This illegitimate use of the term had, and has maintained, a popular appeal. So popular is the term "colitis" that no other one will satisfy many patients who have a functional disorder of the colon. Recently, however, "colitis" has lost some of its appeal. The "allergists" have opened a show on the same lot, and by making skin tests "prove" to the satisfaction of the unfortunate patient that his discomfort is attributable to being sensitive to protein or other foods. I know of one patient who was convinced that she was sensitive to sixty-one foods. The theory of alleged allergy to food is most gratifying and convincing to those patients who have, as a part of their functional colonic disorder, sitophobia. It gives them an objective reason to insist on odd dietary regimens. At the present time, one cannot avoid the impression that infection, allergy to food, and the like can be important etiologic factors in only a small percentage of the total number of functional disorders of the colon.

The etiology of functional disorders of the colon is a mirror image of the hereditary taints, congenital endowments, physical and mental attainments, and abuses since birth. That is, the symptoms may be referable to the colon but the etiology is extrinsic. The various functional disorders of the intestine, which have been described under various headings, such as "spastic colitis," "nervous diarrhea," "mucous colitis" and many other terms, are phases of one and the same disorder. The etiology of this disorder may vary widely. Some of the etiologic factors are systemic diseases with colonic symptoms, environment, tear of disease, laxatives, allergy, irregular habits, hereditary, and congenital malformations. In all cases of functional disorder of the colon there are varying degrees of fatigue, fear,

anxiety and a general failure of relaxation, which are combined with one or more of the foregoing factors. The limits of the presenting complaints are the limits of the human imagination, but, in the opinion of the patient, the bowels always occupy a paramount position in the production of physical discomfort. Systemic disease is the paramount issue to be made in all cases of suspected functional disorders of the colon. The symptoms of a functional disorder may be impossible to distinguish from those that would be present if there was some underlying organic disease. Noteworthy of the diseases which in their early stages or during their progress may be confused with functional disorders are pellagra, mild regional ileitis, and certain forms of sprue. Pernicious anemia associated with achlorhydria may also be confusing. Chronic poisoning with heavy metals, such as lead, which produce obstinate constipation and intestinal colics, combined with the abuse of the bowel by the use of strong purgatives and enemas may produce symptoms which will require careful and appropriate studies in order to make a differential diagnosis. During the course of many diseases, such as exophthalmic goiter and Addison's disease, the functions of the intestine may be deranged. Fevers, infectious diseases, septicemia, malnutrition from any cause, pelvic and abdominal tumors, deranged functions of the pancreas, liver and kidneys are at times accompanied by colonic symptoms to the degree that the underlying disease is masked.

**Environment.**—The surrounding conditions, influences or forces which hem in and daily influence the thoughts, actions and the physical activity of any person may be disagreeable enough to be inciting factors in the production of functional disorders. An environment of poverty, if the patient is accustomed to it, is conducive to the development of organic digestive disorders; whereas, an environment of luxury, especially if newly acquired, such as by the marriage of a poverty-stricken young woman to an elderly wealthy bachelor, is ideal for the development of functional disorders of the colon. One might argue that the example just cited was on the basis of sex. In certain instances this may be true, but not always. Family disagreements, social aspirations, ambitions by mothers for attaining the "greatest opportunity" for their children are common environmental factors of importance. Examples of an



environment in which sex may play an important rôle are seen among young women who have had college romances which have terminated unhappily. After the glamour of college life is over they are forced to retreat to a village or rural community to teach school where there are no "eligible" young men. The sex instinct under environmental influences is of the greatest etiologic importance in the marriage of a frigid, fearful woman to a robust philandering husband. A changing environment is of the greatest importance, especially when the changes create surroundings which are incompatible with the physical and mental qualifications of the patient.

**Fear of Disease.**—Fear is an important etiologic factor in the production of functional colonic disorders. However, here the consideration will be limited to the fear of disease. The fear of disease has found a tangible ally through advertisements of remedies to prevent auto-intoxication and colitis. These advertisements may be very suggestive in their implications as to the prophylactic and hygienic qualifications of the remedies in the treatment of these spurious conditions. The fears of the patients should be treated with the greatest of caution and sympathy by the physician. If the physician assumes a jocular attitude toward these patients, they will be driven into the hands of a sympathetic individual who will employ ill-advised and infamous treatments which will result in the subsequent development of unmanageable disorders of the colon. Nothing should be spared in the way of sympathy and examinations to convince these patients they do not have organic disease. In families in which one or more members have suffered from disseminated polyposis or carcinoma of the colon or rectum, or from chronic ulcerative colitis, a fear of these maladies is a natural human tendency. This fear is often precipitated by the presence of mucus in the feces. Mucus is a normal but variable secretion of the colon and not a sign of disease. This fact is worthy of great stress to those who fear its presence in their feces.

The patients who suffer from functional disorders which result from the fear of disease of the colon or elsewhere in the body may be classified in two groups. The first group comprises those who are intelligent and who have a good sound basis for their fear, such as an unexplained diarrhea following

a recent attack of pulmonary tuberculosis or time spent in a tropical climate. The second group includes patients whose judgment is fallacious. Their conception is that they have a disorder of the bowels; their complaints and their "case" is different from any the physician has ever seen. They are worthless to themselves, miserable, arrogant, evasive and difficult, if not impossible to treat successfully. The patients in the first group, however, are both amenable and amendable.

**Laxatives.**—The use of laxatives is as old as the human race itself. It seems to be almost instinctive for carnivorous or near carnivorous animals, such as man, to empty the stomach and intestines when they do not feel well, that is, the dog may invoke vomiting by eating grass. These facts make it easy to understand that the human race as a whole is easy prey to the alleged beneficial effects of "liver pills." When the colon has been emptied with a laxative, it fills up with liquid feces and gas. If there is any tendency to irritability, the presence of the gas and fluid will produce discomfort. This discomfort will be greatly enhanced by the repeated emptying and the resulting stimulation of the bowel by the laxative. It is doubtful, however, that the repeated use of laxatives by normal individuals would produce anything more than a mild functional disorder of the colon which would recover as soon as purgation was discontinued. In the habitual use of purgatives the colon is punished because of erroneous ideas of its proper function.

**Allergy to Food.**—In recent years much attention has been directed toward the possibility that many persons who have an irritable colon might in reality be suffering from an allergy to food. In so far as the total number of these patients is concerned, a relatively small percentage of them will respond favorably to the so-called elimination diets or will give positive dermal or intradermal tests with food extracts. There are very definite rules which should be kept in mind when it is thought necessary to make a survey of foods for possible detection of allergic phenomena. The patient should have: (1) symptoms which can be explained by spasm of smooth muscle, (2) other manifestations of allergy, (3) positive family history for allergy, (4) positive skin tests, and (5) eosinophilia. If a patient does not present these findings one is left to the un-

certainities of "elimination diets." The interpretation of the results obtained when an elimination diet is employed is wholly dependent on the patient's interpretation of the effects of foods. The physician's opinion may be unscientific if a possible easy chance to please the patient arises. The results, therefore, are influenced by two uncontrollable errors: (1) the patient's interpretation that foods are harmful, and (2) the physician's estimation of the improvement. Certainly, such evidence is not good in a disease in which sitophobia may be a prominent symptom.

**Irregular Habits.**—Irregular habits, especially bowel habits, are a most important etiologic factor in the production of a functional disorder of the colon in cases in which there is a tendency toward constipation. A certain degree of relaxation during work, sleep, and periods of full relaxation such as obtained while on a good vacation are necessary as well as a normal bowel movement and the development of the habit of a regular time for visits to the toilet. Irregularity prevents relaxation and annuls sensations. A sizeable percentage of functional disorders of the colon would cease to exist if regular habits of eating, sleeping, going to the toilet, and physical exercise were instituted. When there is an increased number of bowel movements during the day, regular habits for meals without extreme temperatures of foods and beverages may be most beneficial. Ingestion of hot or ice-cold materials increases the so-called gastrocolic reflex. Loose bowel movements are therefore to be expected if such indiscretions are practiced. In cases in which the gastrocolic reflex phenomena are extreme, ingestion of foods at body temperature on a fasting stomach will incite repeated bowel movements. An indeterminate number of habits practiced by these patients are so deeply seated through environment that the patients are not aware that what they do is wrong. Such habits cannot or may not be elicited in taking the clinical history.

**Heredity.**—The immeasurable composition of the patient is of the greatest importance, especially in cases of functional disorders of any kind. The physical stature of the parents greatly influences that of the offspring. The same is true of mental habits, conduct, hours of sleep, foods and drinks. Heredity, environment and habits are so intimately associated

and interwoven in the same individual that analysis by the average physician is impossible. If such an analysis is successfully made it will not change hereditary equipment. A painful functional disorder of the colon is rarely seen in the sturdy, muscular blonde. The tall, scant brunette with a "stylish figure" is the characteristic build to have a "spastic colitis" or "visceroptosis." Heredity plays an important rôle in all the foregoing etiologic considerations. It is regrettable, however, that the biologic or genetic data are insufficient to permit interpretation of the suspected hereditary factors in this disease. The congenital endowments of a person refer to certain mental and physical traits or peculiarities which existed at the time of birth. At birth one either possesses the type of nervous system of the stoic person or that of the "high strung," "nervous," irritable person. To these congenital attributes may be added the hereditary factors, which may be either beneficial or harmful, and the influences of environment, which also may be similarly interpreted. The hereditary and environmental factors may influence but not change the fundamental congenital endowments; that is, the nervous system which will manifest its control over the body by the production of a functional disorder of the colon is present at birth. One cannot avoid the impression that proper environment and hygiene prevent the physician from seeing many individuals who have the congenital endowments for such a disorder, and that unfortunate environmental influences bring many nearly normal persons to him. A person who has proper congenital endowments cannot have a functional disorder under any circumstances.

The congenital physical endowments are of the greatest importance in a negative way. The well-formed baby who has a gastro-intestinal tract that functions properly at the time of birth does not have any congenital factors of a physical nature that will predispose it to a functional disorder of the colon. That is, the physical structure of the colon does not play any rôle in these disorders. There may be congenital malformations of the colon, which are of two types. If the malformation is of sufficient degree it will prevent function. Congenital malformations such as dolichocolon, redundant sigmoid flexure and visceroptosis are of no etiologic importance.

### TREATMENT

The treatment of functional disorders of the colon, since the etiology is mainly extrinsic to the alimentary canal, must be directed toward the source of the disorder. Treatment is individualistic and must be outlined for each case. These patients insist on consulting the most successful physicians in the community. Such a physician often does not have time to spend in taking a long history and carefully pointing out the insignificance of their symptoms. These patients should never be told that they are only "nervous." Such a statement has no therapeutic value, and may serve to make the patient feel that the physician lacks interest. If possible, one should be sure that all fear of organic disease is removed. A thorough search for organic disease is reassuring to both the patient and the physician. It creates mutual confidence. The phenomena of pain are best explained on the basis of fatigue and increased sensitivity and susceptibility of the nervous system, which are produced by the failure to relax. The presence of mucus in the feces is not the result of infection in the bowel, but is evidence of deranged secretory function of the colon as a result of increased sensitivity and irritability.

The inspection of the feces is instinctive in man. This is an instinct of error when it is done with an idea of appraisal of digestive function. In reality, about 80 per cent of the mass of the feces represents dejecta from the alimentary tract and only 20 per cent represents the residue of undigested food. This residue consists of foods which are not digestible by the human alimentary system.

The greatest aid in treatment is an orderly consideration of the etiologic factors. The conception that these disorders arise in the colon and can be corrected by special dietary regimens designed to "harmonize" with any evolutionary anatomic or physiologic qualities of the human colon is erroneous. If a diet, no matter how complicated, would relieve the symptoms of this disorder, treatment would be simple and successful. The practical point here is to realize that a sitophobia, at least for some foods, is often present. Under such circumstances it may be difficult to get these patients to take a normal and well-balanced diet. This brings one to the very interesting question as to what is the structure of the human colon and

what are its comparative anatomic structural qualifications which indicate possible potential influences diet might have on the functions. The ideal way to approach this problem would be through a study of the natural foods man has taken during the various stages in his long evolutionary trek. This ideal cannot be obtained. Primitive man ate a great variety of foods, but this is the end of our knowledge. However, mammals in general can be divided into three groups according to the main sources of their natural food supplies. Each of these groups possesses certain definite anatomic alimentary structures according to the main source of food eaten. The first group, the herbivora, which partakes of plants, has, as a rule, an enormous and complicated colon which plays an active part in digestion. A colon with a large volume is necessary for the digestion of cellulose, because this material has to be retained in the body long enough for the enzyme citase, which is in the plant cell, to change the cellulose to simpler compounds—the starches.

The second group consists of the carnivora. If the alimentary structure of the common house cat is contrasted with that of the herbivora, one is immediately impressed with the differences. The structure of the alimentary tube of the cat is simple in design. There are no sacculations, blind pouches or complicated intestinal coils. The simple thick-walled, muscular stomach and intestines, for the most part, are attached to the coiled and lengthened primitive mesentery. The colon, except the cecum, is short, muscular and devoid of sacculations.

The third group consists of the omnivora. With the foregoing very brief anatomic considerations in mind, it may be pointed out that man occupies a position, comparatively speaking, near the carnivora. The alimentary tube of man is simple except for the rudimentary sacculations of the colon. The colon of the herbivora possesses important digestive functions. The colon of the carnivora does not have any digestive function so far as organic digestion is concerned.

In the laboratories at the Clinic, Welch has demonstrated that the colon of man does not possess digestive functions. Its sole function is the absorption of salts and water. Thus, the colon of man, although of a greater capacity than that of the carnivora, like the colon of the latter, does not possess im-

portant digestive functions. There is every reason to be positive that a patient who has a functional disorder of the colon should not be given a diet which contains a large amount of cellulose. There would be a more sound reason to prescribe an all-meat diet. Practical experience teaches that a man may live and even retain his health with a diet of meat or of vegetables. Common sense and instincts teach that such is neither wise nor necessary.

Diets of the omnivora, which are planned to harmonize with the anatomic and physiologic functions of the colon in the prevention of "auto-intoxication" and various other spurious ills, are not in keeping with the known facts. Man has no structural alimentary equipment for the digestion of cellulose. The fact that one can eat "all bran muffins," the husk and debris from all sorts of grain and endure them, is an evolutionary and structural anatomic privilege. Because man is either a facultative carnivore or herbivore does not mean that these attributes should be abused unnecessarily when he is functionally ill. A more severe violation of natural laws than the prescribing or overindulgence in foods such as those with a high content of cellulose is not known. A comparable mistake would be to feed meat to a sick ox.

In those functional disorders characterized by constipation, some dietary adjunct should be resorted to, which will increase the volume of the feces. Such an increase in the volume may be obtained by a material such as agar, which is chemically and physically inactive. This material is indigestible the same as cellulose. However, agar forms a soft gelatinous bulk which consists largely of water, whereas, the cellulose in the food remains hard and may have local stimulating effects similar to a more drastic laxative.

Such general hygienic measures as regular hours, regular periods of relaxation after meals, daily walks, and outdoor sports are to be encouraged. Mild sedatives, such as elixir of phenobarbital, 1 drachm (4 c.c.), administered before meals and at bedtime, may be useful. Tincture of belladonna, if given in proper dosage, may be beneficial to those who have abdominal cramps.

In severe disorders associated with a great number of bowel movements daily, rest in a hospital may be required. Tincture

of opium, camphorated tincture of opium, and the tincture of iodine are at times indispensable drugs in the treatment of these disorders. Generally, the tincture of iodine, administered in doses of 10 minims (0.6 c.c.) in a full glass of water, is of genuine value. A soft diet should be given. Liberal amounts of fluids are required to replace the loss of water through the feces. Evident interest, patience, and optimism on the part of the physician, who most constantly plans the regimen is the most successful plan of treatment.

In the treatment of the various phases of these colonic disorders, the tact and ingenuity of the physician may be given the greatest test. If the physician is resourceful enough, only death of either the physician or the patient, from other causes, will end the battle. No one can hope to be resourceful enough to treat more than some of these patients successfully. However, those who are successfully managed should be a great source of joy and are worthy of reflection as a professional accomplishment.

#### SUMMARY

All the functional diseases of the colon are phases of the same disorder, which has an etiology extrinsic to the bowel. The severity of these disorders may be measured by the ease with which the colon may be provoked to change its habits so widely. Of the etiologic factors, fear, anxiety, fatigue, and a failure to relax are present in varying degrees in all cases. These constant causes are usually associated with such factors as fear of disease; hereditary taints, congenital attributes, allergy, and the use of laxatives. These etiologic factors are often difficult to elicit and their discovery requires time and considerable patience. The treatment is difficult; it consists of convincing the patient that further search of the mystic and unusual etiology serves only to deplete his health. A reasonable diet and regimen for improvement of the general health are the therapeutic agents par excellence. These measures will rehabilitate all those who are really desirous of as near a normal existence as is possible to obtain, but will not cure any of them. These patients have sustained irreparable damages; fatigue, fear, anxiety, and a failure to relax will always produce a relapse. This point should always be made clear to the patient.



The dietary management of these functional disorders consists of: (1) overcoming whatever sitophobia that may be present; (2) an adequate, well-balanced diet which includes minerals, vitamins, and an adequate number of calories, but which does not contain large quantities of cellulose. The cooking of starches renders them more digestible, which is desirable in cases in which the patients are undernourished and have diarrhea. In other words, a minimal amount of raw fruits and vegetables should be given.

The bulk of the feces is alimentary dejecta and not food residue. A soft bland residue, such as is obtained by the administration of agar, is desirable to increase the bulk of the feces in cases of constipation. There are a great number and variety of these materials on the market, which will furnish a soft nonirritating bulk to the feces. The selection of such a substance should be made with great care since laxatives frequently have been added.



## VITAMIN DEFICIENCY DISEASES: THEIR DIAGNOSIS AND TREATMENT

DWIGHT L. WILBUR

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It is sometimes difficult to appreciate the fact that ill health and disease may result from deficiency or lack of some essential substance. It has been taught for many years that diseases result from an abnormal factor, such as bacterial or other toxins, growth of tumors or trauma, and only in the past forty years has the concept of deficiency disease arisen. Pellagra, beriberi, scurvy and rickets, which now are recognized as deficiency diseases, were at one time thought to be results of intoxications of various types. The later correct concept of deficiency diseases was based on the discovery of those things in foods which are essential for the health of the individual. Clinical and experimental evidence has indicated clearly that vitamins are not only essential for the preservation of health, but that a normal food supply furnishes them in adequate amounts. Although an insufficient intake of protein and certain minerals in the diet will produce states of deficiency, the term is generally used in relation to states of vitamin deficiency.

Most people have become vitamin-conscious, and while physicians in general recognize that disease such as xerophthalmia, beriberi, and scurvy are rare, nevertheless they are constantly reminded, particularly by advertisements, that failure to maintain an adequate intake of this and that food containing vitamins will lead to a variety of diseases. Emphasis is persistently placed on the probability of occurrence of mild states of vitamin deficiency, difficult of recognition, and responding to specific vitamin therapy. Consequently, every wise clinician is continually on the lookout for states of vitamin deficiency among the patients he sees.

There is considerable experimental evidence, substantiated in part by clinical experience that states of partial deficiency

are not uncommon, and that the "optimal" requirement of a vitamin is much higher than the "minimal" or actual requirement.

It is interesting to observe, in the United States at least, that the principal concern with regard to the production of deficiency diseases is not so much because of an insufficient quantity of food as it is because of the preparation of foods in highly concentrated and purified form, such as flour, prepared oils, foods "ready to serve," and so forth. Although such preparation of food has many benefits, it has limited the amount of food taken in the natural state, and it is in the natural state that foods are richest in vitamins. In the past few years the economic depression has, in some instances, reduced the ability of people to obtain foods in a natural state, because many such foods are perishable and therefore expensive.

The importance of the gastro-intestinal tract in relation to the development and occurrence of deficiency diseases is continually being emphasized. It seems reasonable to believe that, in the United States, a considerable proportion of deficiency states will be found to arise as a result of abnormalities of digestion and alimentation. Changes in the gastro-intestinal tract which lead to failure of adequate absorption, no matter what the cause, may lead to deficiency diseases even though the diet contains an adequate supply of essential substances.

#### VITAMIN A

The most readily appreciated clinical symptoms of vitamin A deficiency have to do with changes occurring in the eyes, and consequently in previous years this deficiency has been considered to be manifested chiefly if not entirely in this way, in fact, for years vitamin A was known as the anti-xerophthalmic vitamin since xerophthalmia occurred in vitamin A deficiency.

It seems clear that vitamin A is closely related to the yellow pigment, carotene, which is widely distributed in nature and is found in carrots, squash, yellow corn, and other vegetables. Carotene is the chemical precursor of vitamin A, which is the primary alcoholic derivative produced by the symmetrical division into two parts of the beta-carotene molecule. Vitamin A is probably a catalyst in its chemical action, and physio-

logically it is essential for the maintenance of the integrity and normal state of all epithelial tissues. When vitamin A is present in insufficient quantities the epithelial tissues lose their normal appearance, and thickening or keratinization, followed by secondary infection, result.

**Night Blindness.**—Deficiency of vitamin A may lead to night blindness or inability to see clearly in dusky light; this is not an uncommon occurrence in the Orient but it is unusual in the United States. This condition may be defined as difficulty or inability to adapt vision to faint illumination, and it may result from intra-ocular lesions as well as from deficiency diseases. Jeans and Zentmire have studied the sensitivity to light following partial adaptation to darkness of school children in Iowa, and reported (1934) that about 20 per cent of the children who had subnormal vision in the dark were relieved promptly by partaking of cod liver oil; in a later report (1936) they found that with the same test, 20 per cent of a rural group, 53 per cent of a village group, and from 56 to 79 per cent of an urban group of school children presented evidence of vitamin A deficiency.

**Xerophthalmia.**—This condition is manifested by dryness of the conjunctival tissues which, if it progresses, may lead to conjunctivitis, keratomalacia or softening of the cornea, and finally to blindness. Bitot's spots, triangular white spots appearing like dense foam of soap in the palpebral fissure, and subsequently light brown pigmentation of conjunctiva, may be present during this transition. Xerophthalmia is of exceedingly rare occurrence among infants in the United States.

**Cutaneous Lesions.**—Since the principal influence of vitamin A is on epithelial tissues, it might be anticipated that cutaneous lesions would occur in vitamin A deficiency. The characteristic change, which is considered by some authorities to be the first manifestation of deficiency, consists of keratinization of a hard, dry papular type that resembles goose skin and is most marked on the extensor surfaces of the forearms, legs and thighs.

**Lesions of the Urinary Tract.**—It has been recognized for several years that if an albino rat is given a diet deficient in vitamin A, keratinization of the epithelium of the renal pelvis develops and frequently urinary calculi of the calcium phos-

phate type occur. Although there is evidence to substantiate the view that in some cases renal lithiasis of man may be related to deficiency of vitamin A, nevertheless the exact etiologic relationship cannot be stated until more information is available.

**Infections.**—There has been much discussion of the relation of vitamin A to infections. In fact, this vitamin has been called the anti-infective vitamin, and much of it is prescribed for purposes of combating infections or for increasing resistance to them. The most important practical problem in this respect is not so much whether a person who is receiving an inadequate diet is less capable of resisting infection than is a normal person, but whether an amount of vitamin A in excess of that normally obtained by well-nourished persons will further increase resistance to infection. Since the only recognized anti-infective influence vitamin A possesses is in maintaining normal epithelium which will act as a barrier to infection, and since so far as is known the vitamin does not have any influence on immunologic processes, it seems obvious that vitamin A in reality is not an anti-infective vitamin.

**Miscellaneous.**—Effects of deficiency of vitamin A on tissues other than those already considered have been described. Thickening of epithelial layers of the respiratory and gastrointestinal tracts have been reported, and cysts or acute and chronic inflammatory changes may develop. The relation of vitamin A to changes in the nervous system is questionable. In the experimental animal an insufficient intake of the vitamin may lead to failure of growth, but this apparently is not a significant clinical feature of deficiency of vitamin A in man.

**Diagnosis.**—The clinical diagnosis of vitamin A deficiency is not easy. In the rare case in which xerophthalmia is present, and in which this deficiency is marked, with features noted in the foregoing, the diagnosis may not be difficult if it occurs to the mind of the examining physician. The principal interest at present is detection of states of mild or partial deficiency. When the physician is confronted by a patient whom he suspects may have vitamin A deficiency, he should inquire into the presence of night blindness, and on examining the patient he should look for dryness or pigmentation of the conjunctiva and a papular cutaneous eruption involving particularly the limbs, especially the extensor surfaces. Patients who have

night blindness usually complain that it is impossible for them to see in the twilight, at night, or in a darkened room which they enter from the sunlight. They are likely to bump into objects when walking at night. If examination of the fundus of the eyes does not reveal retinitis pigmentosa or other intra-ocular cause for night blindness, the probability is great that the night blindness is of the essential type and is caused by nutritional abnormalities.

If any of the symptoms noted are present, or if they are absent, and vitamin A deficiency is suspected, two other examinations may aid in determining the presence of this condition. The first is a study of the sensitivity to light following partial adaptation to darkness, as described by Jeans and Zentmire. Such an examination requires special equipment and experience, although if these are available, the test is simple. The second method consists of scraping the bulbar conjunctiva, making smears and examining them for keratinized epithelial cells. If either of these tests is positive or any of the previously noted symptoms are observed, it is reasonable to suspect that vitamin A deficiency is present. Confirmation is obtained if these signs disappear following administration of vitamin A or carotene. Until more satisfactory methods are available for determination of vitamin A in tissues, and until more is known of the physiology of the substance, physicians will have to depend on relatively indirect methods to determine the presence of vitamin A deficiency. If patients have renal calculi or suffer from repeated infections, and vitamin A deficiency is suspected, observations and examinations, as previously noted, may be of some value in suggesting, but not proving the presence of vitamin A deficiency.

**Treatment of Vitamin A Deficiency.**—Deficiency of vitamin A usually may be prevented by the use of adequate amounts of the following foods rich in vitamin A or carotene: butter, cream, cod liver oil, carrots, eggs and spinach. Fish liver oils are rich in vitamin A, particularly those of the halibut, cod, burbot, and tuna.

The daily requirement of vitamin A is not known, but is probably in the neighborhood of 6,000 to 10,000 U.S.P. units. In the treatment of vitamin A deficiency states the following measures are of value: (1) a diet high in content of foods

rich in vitamin A; (2) supplements to the diet of vitamin A in cod or halibut liver oil or carotene in amounts of at least 10,000 U.S.P. units daily; (3) in rare instances by intramuscular injection of cod liver oil or other substances rich in vitamins.

### VITAMIN B<sub>1</sub>

Vitamin B<sub>1</sub>, the antiberiberi or antineuritic vitamin, also known as vitamin B, which has been prepared in crystalline form, is widely distributed in foods. While apparently a catalyst in its chemical activity, physiologically it is essential in the metabolism of carbohydrates, having some part to play, it is thought, in the oxidation of lactic and pyruvic acids. In vitamin B<sub>1</sub> deficiency, there is an abnormality in the pyruvic acid metabolism of nerve tissue which in part is responsible for the disturbances of the nervous system and for degeneration of the peripheral nerves accompanying this condition.

**Multiple Neuritis.**—Deficiency in vitamin B<sub>1</sub> results in multiple neuritis and although it is one of the characteristic features of beriberi, it may occur separately without other features of beriberi, or it may occur in association with other symptoms. There are no clinical features which distinguish the peripheral neuritis of alcoholism from that observed in pregnancy, or in beriberi, or in association with gastro-intestinal disturbances such as chronic diarrhea and vomiting. Recent evidence indicates that in many cases the neuritis which occurs in cases of chronic alcoholism and during pregnancy is the result not of alcohol or toxemia, but of a deficient intake or loss of vitamin B<sub>1</sub> that accompanies these conditions. Efforts have been made to relate many other types of peripheral neuritis to a deficiency of vitamin B<sub>1</sub>, as yet with only partial success.

**Beriberi.**—Beriberi, a disease common in the Orient, is rarely observed in the United States. The characteristic triad of symptoms is edema, peripheral neuritis, and cardiac failure. Although the presence of all of these symptoms would assure the diagnosis, they may not all be present. The cardiac symptoms usually occur as a result of failure of the right side of the heart, which is hypertrophied and dilated. Tachycardia is common, fever is often present, and a variety of the symptoms



may occur, including anemia with macrocytosis of the erythrocytes.

**Changes in the Gastro-intestinal Tract.**—A deficiency of vitamin B<sub>1</sub> has been reported to produce atrophy of the papillæ of the tongue, achlorhydria, and hypotonicity and hypomotility of the musculature of the gastro-intestinal tract. An adequate explanation for these changes is difficult to obtain, although degeneration of Auerbach's plexus may be responsible for the abnormalities in motor function. Anorexia is the most commonly observed gastro-intestinal symptom, but constipation and vague abdominal complaints are not uncommon.

**Changes in the Cardiovascular System.**—Evidence that the cardiovascular system is affected in deficiency of vitamin B<sub>1</sub> is suggested by edema, tachycardia, or bradycardia, which occur in beriberi. Weiss and Wilkins reported that there are certain changes in function of the cardiovascular apparatus in vitamin B<sub>1</sub> deficiency, consisting of simple tachycardia, vagus reflex irritability with bradycardia or with asystole and syncope and failure of the right or left side of the heart, peripheral arteriolar dilatation or vasomotor collapse with vascular constrictions in various combinations. Cardiovascular changes should not be considered as due to vitamin B<sub>1</sub> deficiency unless there is good evidence that the intake of this vitamin has been inadequate or there is associated evidence of the deficiency in other organs.

**Diagnosis.**—The diagnosis of vitamin B<sub>1</sub> deficiency is simple if well-developed beriberi is present. Our particular interest, however, is in states of partial deficiency, and in such conditions the diagnosis is difficult and requires considerable judgment and experience. There are no laboratory procedures which are helpful in determining the adequacy of the vitamin B<sub>1</sub> metabolism of a patient. Recently, Harris and Leong have reported a method by which the vitamin B<sub>1</sub> content of the urine can be estimated quantitatively, but as yet this is not practicable for ordinary clinical use. In some cases in which the diet of the patient is known, an estimation of the adequacy of the vitamin B<sub>1</sub> content of the diet, as compared to the requirement of the patient, may be made by Cowgill's formula. He has shown that the requirement of B<sub>1</sub> is proportional to both intake of calories and body weight.

In searching for clinical evidence of vitamin B<sub>1</sub> deficiency, the physician should keep in mind the symptoms and signs noted in the foregoing, particularly those related to the nervous system and the gastro-intestinal tract. If patients reveal signs of peripheral neuritis, paresthesia of the extremities, tenderness of the muscles with weakness or paralysis, or a sore tongue which may have atrophied papillæ, consideration should be given to the previous diet and to the presence of gastro-intestinal disease which might interfere with adequate nutrition. Great care must be exercised in a given case before attributing anorexia, or other gastro-intestinal symptoms to vitamin B<sub>1</sub> deficiency.

**Prevention.**—It has been estimated that the normal intake of vitamin B<sub>1</sub> for an adult man is 1 mg. daily or 250 to 500 International Units. Since the vitamin is widely distributed in foods, it seems likely that only in cases in which the diet is exceptionally limited will deficiency of vitamin B<sub>1</sub> occur. In cases of chronic alcoholism in which the diet is restricted markedly for a considerable time, deficiency of vitamin B<sub>1</sub> is probably not infrequent. Although there is a suggestion in the work of Williams and his associates that vitamin B<sub>1</sub> deficiency may be far more common than previously has been thought, proof is still lacking. The prevention of vitamin B<sub>1</sub> deficiency lies in the intake of an ordinary well-balanced diet.

**Treatment of Deficiency.**—In the treatment of vitamin B<sub>1</sub> deficiency, a variety of therapeutic methods is available. Foods high in vitamin B<sub>1</sub> content are yeast, fresh vegetables, whole cereals, and milk. Preparations of brewers' yeast in powdered or tablet form, and concentrates and crystals of vitamin B<sub>1</sub> are available for therapeutic use. The crystals may be administered intramuscularly in solution or orally. Spies has emphasized, particularly, in the treatment of pellagra, the advisability of giving exceedingly large doses of vitamin preparations. This same principle probably holds in other vitamin deficiency states. It would be advisable, in a state of vitamin B<sub>1</sub> deficiency, to give 25 gm. of powdered brewers' yeast (such as Harris') one or four times daily, depending on the degree of deficiency, along with a diet containing 4,000 calories and rich in vitamin-containing foods. The minimal therapeutic dose of vitamin B<sub>1</sub> is probably about 10 to 20 mg. daily, and

synthetically prepared crystals are now available at a reasonable cost. One advantage of giving yeast or a similar preparation in place of, or in addition to, the vitamin in crystalline or concentrated form is that, although marked relief is obtained in deficiency states from administration of vitamin B<sub>1</sub> in this form, complete relief is generally not obtained until yeast or some substance containing all the factors of the old water-soluble vitamin B is given. Yeast contains apparently an essential substance which is not present in the crystalline and concentrated forms of vitamin B<sub>1</sub> or in B<sub>2</sub> (G).

### VITAMIN C

Vitamin C, which chemically is ascorbic acid, also known as cevitamic acid, is the antiscorbutic vitamin. More is known of the metabolism of this vitamin than of any other, and in recent years evidence has been accumulating that it is related not only to scurvy but also to dental caries, hemorrhagic diathesis, and anemia. Its relation to acute infections, particularly rheumatic fever, and its place in resistance to infection are uncertain. Vitamin C is a powerful reducing substance, and physiologically is essential in the formation and maintenance, in a normal state, of intercellular substance, particularly of the blood vessels, dental forming organs, and connective tissue.

**Scurvy.**—Scurvy is uncommon in the United States, but it is observed occasionally among infants. The fundamental pathologic change is in the intercellular substance, particularly of the blood vessels and bones, with softening, which leads to hemorrhages into the subcutaneous, subperiosteal, gingival and other tissues. It has been observed that the intercellular substance, which ordinarily exists as a solid or gel, under circumstances of vitamin C deficiency may become a liquid. Early signs in the development of the disease are fleeting pains in the extremities, spongy and readily bleeding gums followed by evidence of hemorrhage into the skin and subperiosteal tissues, particularly of the long bones.

Considerable interest lately has been given to "latent" or "preclinical" scurvy. The clinical features of this condition include dental caries in children, a hemorrhagic tendency which may express itself in hemorrhage from any organ, subcutaneous

petechiæ, a positive capillary resistance test, and a variety of indefinite symptoms, such as fatigue, pallor, underweight, frequent infections, anemia, and fleeting pains in the extremities, which usually are mistaken for rheumatism.

**Dental Caries.**—Dental caries is frequently observed in experimentally produced scurvy, and clinically it has been considered by some observers to be one of the earliest signs of latent scurvy. Vitamin C is essential for the functional activity of certain cells necessary for formation of teeth, especially odontoblasts and cementoblasts, and it prevents their premature degeneration. When insufficient quantities of vitamin C are present, caries may occur. Although it has been suggested by Hanke and others that dental caries is caused mainly by lack of vitamin C in the diet, this opinion is not widely held. The actual incidence of caries from this cause is still not clear, and there are no gross signs characteristic of this type of caries. If the vitamin C deficiency is marked, the adjacent gums may be swollen, red, spongy, and bleed easily.

**Hemorrhagic Diathesis.**—Great interest has been shown in the relation which may possibly exist between vitamin C deficiency and a tendency to hemorrhages. It is well recognized that there is a hemorrhagic tendency in scurvy which is caused, as noted previously, by abnormalities of the intercellular substances of the capillaries and perhaps also by changes in the blood. Whether one can relate, to vitamin C deficiency, isolated or repeated so-called idiopathic hemorrhages from the nose, gastro-intestinal tract, urinary tract, uterus or other tissues, when signs of vitamin C deficiency other than the hemorrhages are lacking is a question much discussed at present, but still unanswered. In this connection there has been much discussion of the capillary resistance test. It still remains to be proved that this measure is accurate in its portrayal of vitamin C deficiency, and it undoubtedly will be superseded soon by estimations of the vitamin C content of the blood and urine and vitamin C tolerance tests.

**Anemia.**—Presnell has noted a reduced number of platelets and anemia, and Minot has emphasized the occurrence of normocytic or slightly macrocytic anemia in states of deficiency of vitamin C. Reticulocytosis of patients with infections following administration of large quantities of vitamin C has been reported by Faulkner.

**Miscellaneous.**—The relation of vitamin C to the endocrine glands and particularly to the suprarenal glands, is still uncertain. Vitamin C is abundant in the suprarenal cortex and medulla, but its direct or indirect relation to the hormones of the suprarenal gland is still not clear. There has been considerable interest in the possible relation between vitamin C and infections, particularly rheumatic fever and perhaps chronic infectious arthritis. Although changes in the joints similar to those observed in these conditions have been observed in animals which receive diets deficient in vitamin C, there is much evidence against a direct etiologic relationship between deficiency of vitamin C and rheumatic diseases. The clinical value of vitamin C in combating infections of any type is still uncertain, although laboratory evidence suggests that the vitamin may have certain detoxifying properties.

**Diagnosis.**—The diagnosis of scurvy is relatively simple in a well-developed case. The spongy, bleeding gums, painful extremities, and evidence of subperiosteal, subcutaneous, and other hemorrhages are diagnostic signs. The diagnosis of latent or preclinical scurvy is difficult, but suspicion should be aroused if patients reveal considerable dental caries, have unexplained hemorrhages of any type or in any situation, or have long-continued infections. Persons who have used little citrous fruit, tomatoes, milk, and fresh fruits and vegetables may have, or may develop, latent scurvy. It is exceedingly important to emphasize that such conditions do not establish the diagnosis, but only suggest the possibility of it.

Fortunately, physicians possess better methods of determining the presence or absence of partial deficiency of vitamin C than of any other vitamin. The use of capillary resistance tests, estimations of the content of vitamin C in the blood and urine, the use of vitamin C tolerance tests, and estimations of vitamin C saturation are all valuable in this connection. In addition, a therapeutic test in which ascorbic acid is given may produce presumptive evidence of previous deficiency of this vitamin.

If the physician will bear in mind the symptoms previously enumerated as occurring in vitamin C deficiency, the first step to a diagnosis will have been made. The next step perhaps is performance of the capillary resistance test. This is rela-

tively simple and can be performed in the office by marking an area on the skin, 60 mm. in diameter, in the antecubital fossa of one forearm. Following this, venous stasis is produced for fifteen minutes with a sphygmomanometer cuff at a pressure of 50 mm. of mercury. If more than eight petechiæ develop on the marked area, the test is positive; if less than five develop, it is negative. Although this test is not specific, it is suggestive, and, if positive in a case in which vitamin C deficiency is suspected, it should lead to studies either of vitamin C saturation or a therapeutic trial with vitamin C. The quantitative estimation of vitamin C in the urine is relatively simple and can be performed after the method of Harris and Ray with the indicator, dichlorophenolindophenol. At present data are insufficient to permit evaluation of the estimation of vitamin C in the urine excreted during twenty-four hours. The amount excreted depends on the intake and on the saturation of the tissues. Youmans and others reported that an excretion of 20 mg. of vitamin C per day is the lower limit of normal in adults. Estimation of the vitamin C content of the blood is still of uncertain value. Although Abt and his associates expressed the belief that the values they obtained for the reduced cevitamic acid content of the blood plasma will prove a convenient, rapid and accurate method for the detection of subclinical scurvy, this opinion remains to be confirmed. Probably in the future the use of tolerance tests, or of methods of determining the saturation of the tissues with vitamin C will prove most valuable in determining latent scurvy. For example, Youmans has estimated that if a test dose of 600 mg. of vitamin C is given, at least 30 per cent should be excreted in the urine of a normal individual in twenty-four hours. Further observations are necessary before standards are established in this rapidly developed field.

**Prevention.**—Scurvy or vitamin C deficiency may be avoided by intake of a diet adequate in fresh fruits, particularly of the citrous variety, and vegetables. In infants, this is readily accomplished by the almost universal use of orange juice or a substitute. The minimal intake of vitamin C necessary to prevent signs of deficiency is not certain, but probably approximates 20 mg. daily. Occasionally much larger quantities apparently are necessary; it was necessary to give one patient 200 mg. daily to prevent hemorrhagic tendencies.

**Treatment of Deficiency.**—The diet should be high in its content of fresh vegetables and fruits, particularly citrous fruits. This may be supplemented by the administration of vitamin C, in synthetic crystalline form, by mouth or intravenously; from 50 to 200 mg. or more daily should be sufficient in therapy. When given intravenously, solutions of the sodium salt of cevitamic acid approaching approximate isotonicity can be used; that is, 1 per cent of the salt dissolved in physiologic salt solution or 3 per cent dissolved in distilled water. If only the acid is available, it should be neutralized with half its weight of sodium bicarbonate in physiologic salt solution or water before it is injected.

### VITAMIN D

Vitamin D, which is the antirachitic vitamin, is probably the one best known by the layman because it is widely advertised. Rickets is such a widespread disease of infants in the northern hemisphere that it could be classified as probably the most common deficiency disease. Seven chemical substances have been shown to possess vitamin D activity, and consequently the vitamin is not a single chemical substance. Physiologically, the vitamin plays an essential part in the metabolism of calcium and phosphorus, having to do with the retention of calcium and phosphorus in the body as a whole, in the deposition of calcium and phosphorus in the bones, and perhaps in the concentration of these elements in the blood. Calcium, phosphorus, vitamin D and parathyroid hormone are essential for mineralization of normal bone, and the individual part played by each in this metabolic process is still not clear.

**Rickets.**—Deficiency of vitamin D results in rickets, and it has been stated that from 50 to 90 per cent of infants have signs of rickets. The fundamental fault in this disease is failure of adequate mineralization of the bones. The earliest symptoms are usually restlessness, irritability, and head sweating, which are followed by enlargement of the costochondral junctions and formation of the "rachitic rosary." The head may become enlarged and square, the fontanels may remain large, and softening of the parietal bones often results. The epiphyses of the wrists are often enlarged. Weakness of the

muscles, tardy dentition, and spinal curvature may be accompanying signs. The roentgenologic features of the long bones are characteristic; they are first observable at the lower epiphysis of the ulna and femur, and consist of broadening and concavity with irregularity of the epiphysis. There is less density or calcification of the bone than in the normal. Characteristic changes in the chemical constituents of the blood may occur, with decrease in the percentage of inorganic phosphate.

**Osteomalacia and Osteoporosis.**—Osteomalacia or adult rickets has frequently been reported in China but is not observed in the United States. Osteoporosis, however, is not of infrequent occurrence, but it is difficult to judge in the isolated case if it results from abnormality of calcium, phosphorus, parathyroid, or vitamin D metabolism. Not infrequently, in association with celiac disease, there may be osteoporosis, secondary probably to interference with absorption from the bowel of calcium or vitamin D. The recognition of osteoporosis depends entirely on roentgenologic examination. It frequently is associated with pain in the spinal column and shortening of the body height.

**Tetany.**—Tetany may accompany rickets, or it may be associated with celiac disease or sprue which interferes with absorption of calcium, phosphorus, and vitamin D. Tetany, however, is not the result of vitamin D deficiency exclusively. When osteoporosis and low serum calcium accompany tetany, the diagnosis is most likely tetany caused by insufficiency of calcium or of intake or absorption of vitamin D.

**Dental Caries.**—There is little doubt that vitamin D is essential to normal dentition. An inadequate intake of vitamin D is considered by some workers as the most frequent cause of dental caries. An insufficient intake of vitamin D is not the only mechanism by which dental caries is produced, since caries may occur when intake of vitamin D is adequate.

**Diagnosis of Vitamin D Deficiency.**—The diagnosis of rickets is usually simple. When the classical symptoms are present, the diagnosis is obvious clinically. In cases in which the symptoms are less clear cut, the diagnosis may be suspected clinically and confirmed by roentgenologic studies of the long bones.



States of partial deficiency of vitamin D may be suspected if persons have dental caries, tetany, frequently occurring fractures, and osteoporosis of the bones. Patients who have abnormalities of intestinal absorption, such as occur in celiac disease, sprue, and so forth, may present such a deficiency. Whether it is the result of deficiency of calcium or phosphorus or of abnormalities in function of the parathyroid glands may be difficult to determine. The administration of vitamin D may be helpful in distinguishing osteoporosis which is on a basis of deficiency from other types, but it does not necessarily prove that it is attributable to deficiency of vitamin D alone.

It is probable that states of vitamin D deficiency are extremely uncommon among adults.

**Prevention.**—Vitamin D is specific in the prevention of rickets. It may be administered as cod liver oil, viosterol, irradiated milk, or cereals, or by irradiation of the skin by ultraviolet light. Shelling and Hopper reached the conclusion that five drops of viosterol containing about 1,125 U.S.P. units of vitamin D is efficacious in preventing rickets. Jeans reported that an animal source vitamin D in the amount present in one standard teaspoonful of average high-grade cod liver oil or in milk containing 400 U.S.P. units to the quart (1,000 c.c.) is adequate for the infant from the standpoint of retention of calcium and growth.

**Treatment.**—Vitamin D can be administered in a variety of ways. It may be given in fish oils, such as cod liver oil (viosterol), and in a variety of foods, milk, cereals, and so forth. Irradiation of the skin with ultraviolet light will produce vitamin D in the skin, and is useful for the prevention and treatment of rickets. Foods which contain ergosterol, such as milk and cereals, can be irradiated before ingestion, and vitamin D activity may be obtained. Application of vitamin D to the skin results in absorption and utilization of the vitamin.

Therapeutic doses of vitamin D in treating rickets may be in the neighborhood of 20 drops of viosterol (4,500 U.S.P. units), or a similar number of units in other form. In adults with senile osteoporosis, 10 drops of viosterol three times daily in conjunction with 4 gm. of calcium lactate or tribasic calcium phosphate three times daily often will relieve symptoms.

VITAMIN G (B<sub>7</sub>)

Since the demonstration that the original water-soluble vitamin B is composed of several separate fractions, there has been much interest in the character and physiologic properties of the heat stable or antidermatitic factor, B<sub>2</sub> or vitamin G.

For years this vitamin has been mentioned as of etiologic significance in pellagra. Within the last year it has been demonstrated that vitamin G is in fact two substances: one a flavine and the other a supplementary substance contained in yeast extracts and identical with György's vitamin B<sub>6</sub>. The physiologic functions of these two fractions are still not clear; apparently neither alone possesses the growth-promoting action which together they manifest. Recent evidence suggests that the pellagra-preventing factor is the supplementary substance of vitamin B<sub>6</sub>. Singly or together, the two factors are essential for normal functioning of the skin, nervous system, and gastro-intestinal tract.

**Pellagra.**—The etiology of pellagra is still not clear. That a dietary fault exists in most cases seems certain, but whether or not such a faulty diet is the exclusive etiologic agent has not been proved. While it has been generally accepted that pellagra associated with chronic alcoholism, or so-called alcoholic pellagra, is due to inadequate diet, eminent clinicians have previously failed to accept the likelihood that so-called endemic pellagra in the South was exclusively a deficiency disease. However, recent observations of McLester, Spies and their associates indicate that probably most if not all cases of endemic pellagra may be controlled or cured by dietary measures. Although pellagra is common in the South it is not often observed in the North, and when it occurs is often in association with chronic alcoholism and organic disease of the gastro-intestinal tract. This type of pellagra, secondary pellagra, has been noted by Eusterman and O'Leary and other workers, and is of serious prognostic importance, particularly if surgical treatment of a gastro-intestinal lesion is contemplated.

The diagnosis of pellagra still rests on the triad of three d's—dermatitis, diarrhea, and dementia, but these occur simultaneously in severe cases only. Perhaps the most characteristic

feature is the dermatitis, without which the diagnosis is difficult and questionable. The cutaneous lesions consist of dermatitis suggesting sunburn, a reddened, dirty-brown skin, parchment-like, rough and scaly, affecting principally the exposed surfaces, especially the backs of the hands, wrists and forearms, usually in a symmetrical fashion. The face, neck, genitalia and legs may be similarly involved. Gastro-intestinal symptoms which accompany pellagra are variable; diarrhea is the most common in advanced cases and it may be intractable. In less severe cases there may be flatulence, anorexia, vague abdominal distress and at times constipation. Achlorhydria is a frequent finding. Nervous symptoms are not at all uncommon and while dementia is characteristic of severe pellagra in the less severe forms, symptoms characteristic of neurasthenia, such as exhaustion, lassitude, and insomnia, may be present. Loss of weight is characteristic. The development of any of these symptoms, when accompanied by dermatitis of the type mentioned, should suggest the possibility of pellagra. It is wise to examine the stomach and colon of patients for evidence of organic disease if they have pellagra and apparently have been on an adequate diet, or who because of gastro-intestinal symptoms are unable to eat normally. Not infrequently obstructing lesions, particularly malignant ones, or evidence of ulcerative colitis will be found.

**Treatment.**—Despite variability in opinion as to its etiology, the treatment of pellagra is chiefly dietary. The rapid strides which have been made in this respect are well illustrated by Spies, who reported that in the Lakeside Hospital, Cleveland, from 1926 to 1930, 54 per cent of seventy-three patients with pellagra died, despite good care in the hospital. During the past five years Spies and his associates have been able to reduce the mortality to 5 per cent or less among persons who have severe pellagra. The diet should be adequate, the patient should rest, and symptomatic measures should be instituted. In the dietary treatment, Spies has emphasized the importance of very large amounts of foods and preparations high in content of vitamins.

Foods particularly rich in vitamin G are fresh vegetables, especially leafy ones, milk, cream and eggs. Beef, potatoes, and citrus juices are good sources of the vitamin. Yeast and

yeast extracts are especially rich sources of vitamin G, which is also found in liver extract for parenteral use.

In some cases in which vomiting is not present, Spies suggested the use of a well-balanced diet containing 4,000 calories or more, and in addition good brewers' yeast, wheat germ, or liver extract. Good brewers' yeast or wheat germ may be given in doses of 10 to 20 gm. in iced drinks at intervals of three to four hours to make a total of 75 to 100 gm. daily. Liver extract given parenterally in from three to five doses of 20 c.c. each daily is specific, and although expensive is of especial value for patients who, because of a sore mouth or vomiting, cannot tolerate an adequate diet.

Adequate rest with hospital and nursing care is essential in the treatment of severe pellagra. Symptomatic treatment consists of the use of sedatives, antiseptic solutions, such as potassium permanganate, 1:5,000, applied to the skin and tincture of opium in large doses to control diarrhea.

In milder cases in which the diagnosis is uncertain or questionable, the diet should be high in vitamin content and supplemented by 1 ounce (30 c.c.) or more of brewers' yeast or wheat germ, or liver extract given parenterally in doses of 10 c.c. daily.

For patients with organic disease of the digestive tract and pellagra, and for whom surgical treatment is contemplated, the pellagra should be treated before any operative procedures are carried out. Such patients do not stand operations well. The use of liver extract parenterally is of particular value to these patients, since it permits administration of vitamin G without disturbing the gastro-intestinal tract and since the action is rapid.

## THE MANAGEMENT AND TREATMENT OF THE HEART IN SENESENCE

FREDRICK A. WILLIUS

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THE problem of heart disease among persons of advanced years presents certain aspects that are different from those of heart disease in general. In the first place, the problem is narrowed down to a very small group of individuals who selectively have been spared from earlier death from many possible causes. In the second place, the deletion process has greatly reduced the forms of cardiac disease that affect persons of advanced age. Finally, the management of the senescent patient is ordinarily less difficult than is that of younger patients; in the former instance, age has already imposed the necessity of certain physical restrictions, the problem of earning a living has frequently been solved, and there are few, if any, dependents.

It is necessary to establish definite criteria as to what constitutes a normal heart in the late years of life. If one adheres to the criteria which some pathologists have advanced for a normal heart, only the occasional venerable could possibly qualify for a place among this select company. I believe it is only just to recognize the fact that the criteria established for the normal heart at a given period of life must necessarily be modified to meet the dissimilar circumstances at another period. The cardiovascular system, like many other components of the body, participates in a metamorphosis as the succeeding decades of life are encountered. The passage of time and the sustained effect of continuous function, in addition to the variable supplemental stresses and strains of life, inevitably bring about changes in all living things. The most common effects, so far as the heart is concerned, are the sclerotic changes of the coronary arteries and the increased work imposed on the left ventricle by the frequent association of varying degrees of hypertension.

Postmortem examination of patients who are seventy years of age and older practically always reveals evidence of coronary sclerosis. However, these sclerotic changes very frequently are not obliterative in character, and unless obstruction occurs, they may not seriously handicap the function of the heart, especially when the individual has geared his tempo of activity to a level commensurate with his age. The general biologic process of senescence often proves to be a subtle mechanism of self-preservation.

The study of a series of 3,418 cases furnished fairly accurate statistics with reference to the incidence of the eight principal forms of heart disease in the ten decades of life. The forms of heart disease included in this analysis were coronary disease, hypertensive heart disease, rheumatic heart disease, syphilitic heart disease, adiposity of the heart, chronic adherent pericarditis, calcareous aortic stenosis, and congenital heart disease. In 10.7 per cent of the cases the patients were in the eighth, ninth and tenth decades of life; the majority of these patients had coronary disease or hypertensive heart disease. Coronary disease occurred in 5.6 per cent, hypertensive heart disease occurred in 4.4 per cent, while the other forms of heart disease combined occurred in only 0.7 per cent of the entire series of cases.

The sex incidence of cardiac disease which affects senescent individuals is not only of interest but is important. Two separate studies revealed a great preponderance of male patients; in each series of cases the ratio of males to females was 5:1. This discrepancy in sex incidence was to some degree explained by the fact that the number of elderly males who come to the Clinic is greater than the number of elderly females; this is partially explained by the fact that a large number of the elderly men come to the Clinic because of prostatic hypertrophy.

Varying degrees of hypertension is the rule among aged patients; in a study of 700 patients who were seventy-five years of age and older, the value for the systolic blood pressure was found to be 140 mm. of mercury or more in 70.3 per cent of the cases and that for the diastolic pressure was found to be 90 mm. or more of mercury in 40.3 per cent of the cases.

In order to portray the actual pathologic findings in the

senescent heart it seems appropriate to summarize the findings reported in a previous study which was based on the post-mortem findings in 381 cases in which the patients were seventy years or more of age. These cases were selected from a group of 5,751 cases in which the patients came to necropsy. The selection was based on the age of the patients.

Some degree of coronary sclerosis was evident in all of the cases while moderate to advanced degrees of coronary sclerosis were revealed in 72.5 per cent of the cases. Fairly definite parallelisms between the degree of coronary sclerosis and aortic sclerosis occurred, although rather wide variations occurred in individual cases.

Varying degrees of valvular sclerosis occurred in 92.7 per cent of the cases. The valves of the left side of the heart were involved much more frequently than were those of the right side. The mitral and aortic valves were involved in 86.1 per cent of the cases, whereas the tricuspid and pulmonic valves showed involvement in only 13.9 per cent of the cases.

Healed cardiac infarcts were discovered in 4 per cent of the cases and acute cardiac infarcts which had caused death soon after their occurrence were found in 2.9 per cent of the cases.

Occasionally one sees an extremely old patient who has survived coronary thrombosis. In a case recently observed, the patient was a man aged ninety-two years, who had had an attack of coronary thrombosis several months previously, but still was found to be in surprisingly good condition.

Evidence of old, healed endocarditis was disclosed in 3.9 per cent of the cases, but in only 1.1 per cent of the cases was the process marked. Pericarditis occurred in only 3.1 per cent of the cases. This included instances of chronic adherent pericarditis and acute and chronic fibrinous pericarditis. Acute bacterial endocarditis, an incident in generalized sepsis, occurred in 1.3 per cent of cases, syphilitic aortitis occurred in only 0.8 per cent of the cases and in one case carcinoma had metastasized to the myocardium.

It thus becomes evident that the problem of the heart in senescence is chiefly concerned with arteriosclerotic heart disease and hypertensive heart disease, and with their coexistence.

In the management of aged patients the physician must exercise an abundance of tact and diplomacy. He should not

disturb the habits and customs of a long life until he has unmistakably ascertained their detrimental influence. Even then, gradual modification and compromise may be the subtle and successful way of accomplishing the purpose desired. Complete and prolonged rest in bed should be avoided except in the presence of congestive heart failure and acute cardiac infarction, as it is a well-established fact that elderly patients are very intolerant to complete invalidism.

Ridiculously strict dietary impositions are undesirable unless such diseases as diabetes, nephritis and so forth demand drastic changes in the usual intake of food. Marked reduction in diet in order to correct obesity is likewise an undesirable procedure in the senescent period of life. The restriction of fluids is also undesirable unless congestive heart failure with its attendant retention of fluid exists.

In the medicinal treatment of heart disease which affects aged patients, caution must be used in the administration of certain medicinal agents, particularly digitalis. It is a well-known fact that old people do not tolerate the administration of digitalis well and that symptoms of intoxication are likely to appear after the administration of doses that ordinarily would not induce such phenomena among younger patients. This not only applies to such well-known symptoms as anorexia, nausea and vomiting, but particularly to the signs of cerebral intoxication and also to disturbances of cardiac rhythm and conduction. The indiscriminate administration of digitalis to patients of all ages is to be condemned, but its unnecessary employment in the senescent period of life is an unpardonable error. The chief indication for administration of digitalis is congestive heart failure, especially when auricular fibrillation with rapid ventricular rate is present or when the latter is present without cardiac failure.

Likewise, the use of salyrgan should be carefully controlled; however, its skillful employment in congestive failure has repeatedly proved of inestimable value. The determination of renal adequacy is always desirable, whenever possible, before salyrgan is used. A word of warning is desirable regarding the administration of this diuretic to elderly men. It must be remembered that many senescent men have hypertrophy of the prostate gland with partial urinary obstruction and that under



conditions of profuse diuresis urinary obstruction may become complete. Thus, particularly when the urinary output is not considerably increased, careful palpation of the suprapubic region may reveal a greatly distended urinary bladder. Under these circumstances, the introduction of an indwelling catheter becomes necessary.

From time to time, elderly patients who have congestive heart failure may be literally dehydrated in spite of their water-logged condition. The prompt recognition of this fact is of utmost importance, for this situation demands the introduction of fluids in such a manner that they will be rapidly available. It is in such cases that the extremely slow injection of a hypertonic solution of dextrose into a vein is of great value. Dextrose is administered in quantities of 300 to 500 c.c. of a 15 to 20 per cent solution and may be injected into a vein daily or twice daily for several days.

Administration of dextrose likewise has an important place in the treatment of paroxysmal dyspnea. This troublesome symptom frequently accompanies both coronary disease and hypertensive heart disease, which affect the aged patient. The beneficial effect of dextrose is theoretically based on the fact that it replaces glycogen, which is an important constituent of heart muscle. Glycogen is rapidly mobilized under conditions of anoxemia.

Morphine is an extremely valuable drug in the treatment of heart failure; its ability to produce rest and profound sleep in a case in which the patient is restless and wakeful is well known. However, it should be administered cautiously to a senescent patient who has heart disease as it occasionally produces untoward effects. I have from time to time observed Cheyne-Stokes breathing while the patient was under the influence of the drug, but this disappeared promptly when the action of the drug became dissipated. Smaller doses than ordinarily used are desirable and less frequent repetition of the dose is indicated in such cases.

Likewise sedatives such as the barbiturates, amytal and so forth should be administered judiciously, owing to the fact that a mild delirium may occur while the action of the drug endures. The inevitable occurrence of varying degrees of cerebral arteriosclerosis among elderly patients is probably the determin-

ing factor in the production of these undesirable effects. Under these circumstances, the administration of the tincture of opium in moderate doses or the use of chloral hydrate frequently is a satisfactory solution to the problem.

The purine derivatives, such as theobromine, theocin, theophylline, metaphyllin and aminophyllin, can be safely used in such cases when indicated, just as they can in other cases in which the patients are young.

It is, of course, necessary to restrict the physical activities of elderly patients. As previously stated, senescence frequently accomplishes this through such handicaps as arthritis, disturbances in vision and so forth. However, numerous patients are encountered who, through the enthusiastic yet misguided advice of their friends, are encouraged deliberately to seek exercise, and who, with the gusto of the true believer, indulge in ridiculous exertion which is very hazardous and unbecoming to their venerable position in life. There is no doubt that this misguided enthusiasm on the part of many elderly patients results in sudden cardiac death or prolonged heart failure and ultimate death.

In this connection it may be appropriate to recall the story of the old man who had lived for ninety-eight years and whose philosophy of life is recorded in the following narrative. A solicitous friend inquired as to what the old gentleman attributed his longevity. After his usual deliberation he replied as follows: "I never stood when I could sit, I never walked when I could ride and I never stayed awake when I could sleep. In fact the only exercise I indulged in was to be pall-bearer at the funerals of my exercising friends." This point is perhaps well taken, although fictitiously exaggerated.

Nevertheless, with the inevitable premise before us, life is a biologic metamorphosis and the individual who deliberately seeks great longevity, a questionably desirable goal, must voluntarily gear his activity and enterprise to the ever-changing conditions of advancing years. I believe that most people do not seek an endurance record of this type, but desire to participate constructively in life and are only too willing to accept the hazards of such a philosophy.

## DIGITALIS: ITS RATIONAL USE

FREDRICK A. WILLIUS

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NOTWITHSTANDING the fact that digitalis has been used by physicians for a century and a half it is probably the most misused drug in the practice of medicine. Since the days of William Withering, digitalis generally has been conceded to be the most important and the most valuable drug in the treatment of heart disease. The main reason for its misuse probably lies in the fact that we have not as yet thrown off the bonds of empiricism. We have been taught that digitalis is the sovereign remedy in heart disease, and we have been taught also its actions, its methods of administration, and certain dangers regarding its use. Our chief impression regarding digitalis is based largely on the experience that certain patients with heart disease are greatly benefited by the use of the drug. However, if we analyze our experiences with digitalis more fully, we soon recall the fact that we have frequently been puzzled when good results from its administration have not been forthcoming.

The beneficial effects of digitalis in heart disease result from changes the drug produces in the various functions of the cardiovascular system. Many actions have been assigned to digitalis, and many of these have not withstood the test of time and experience, a fact which has undoubtedly contributed to the existing confusion as to its actions and indications. The effect of digitalis on the diseased heart of man is narrowed down to three definite actions, the understanding of which greatly simplifies the indications and contraindications for its use. These three actions are: 1. It depresses the function of the sino-auricular and auriculoventricular nodes, resulting in a tendency to slow the cardiac rate. This is, in part, a vagal action. 2. It depresses cardiac conduction throughout the muscle and increases the refractory period of both the auricles and the ventricles. Depression of conduction, particularly

through the auriculoventricular bundle (His), occurs; this explains the striking effect of the drug in many cases of auricular fibrillation. 3. It increases the amplitude of cardiac contraction. It tends, also, to restore tonus, apparently because of its direct action on heart muscle.

Digitalis does not exert a constant effect on blood pressure; a rise may occur as part of the improvement of cardiac function and general circulation. Likewise, its effect in the production of diuresis is not a result of stimulation of the renal epithelium, as was formerly believed, but again results from the more normal behavior of the renal and the general circulation.

The effect of digitalis on the diseased heart is very different from its action on the normal heart, and also from its effect on the heart of the experimental animal. In order to comprehend the action of digitalis on the impaired heart it is necessary to analyze critically the various actions that the drug may exert, and also to comprehend fully the various underlying disorders leading to heart failure.

Considerable difficulty is at times encountered in definitely establishing the basis of heart failure, and not infrequently failure results from a combination of conditions that must be determined in their proper relationships. The physician is often too willing to rest after he has satisfied himself that a failing heart is the cause of the patient's symptoms, and he may make little, if any, attempt to identify the type of lesion. One of the most important factors in the misunderstanding regarding heart disease and its management has been this apparent indifference to determining the etiologic factor or factors responsible for the existing cardiopathy.

The preparations of digitalis most commonly used are derived from the leaves of *Digitalis purpurea*, although preparations from the leaves of *Digitalis lutea* have been used and are presumed by some to have less tendency to produce nausea and vomiting.

A tincture of digitalis of established potency and of known date of manufacture is a very satisfactory preparation. Its administration is simple, and conveniently permits changes in dosage.

The infusion is the oldest of the preparations of digitalis.

It has been found to be an unreliable preparation, when made by accepted methods, owing to its instability and to the great variations in its potency. Some pharmacists prepare the infusion from the fluidextract, which results in a product of a potency totally different from that of the official infusion and which is no longer comparable to it. An infusion made from the fluidextract has a greater digitoxin content than the official infusion. The relative value of the standard tincture and of the infusion of digitalis has been investigated by Weiss and Hatcher. By their method an infusion of digitalis was prepared that in all respects compared favorably with the standard tincture, and when it was kept in completely filled, hermetically sealed bottles it remained unaltered for nearly two and a half years.

The use of powdered leaves of digitalis in capsules and standard tablets are also satisfactory methods of administering the drug.

Digitalis may be administered intramuscularly or intravenously, although indications for the employment of these routes are less frequently encountered. These methods of administration usually presuppose the presence of an emergency in which the physician has had little or no time for the careful analysis of his patient. It is always possible in a case of acute heart failure that the basis of the condition might definitely contraindicate the use of digitalis. The intramuscular and the intravenous method may be employed with safety when the clinical status of the case is well established, but in the majority of instances it has little advantage over the oral method of administration. Pardee has pointed out that the promptness in action which follows injection is more dependent on the large size of the dose given than on the greater promptness with which the drug comes in contact with the heart muscle. My experience has put me in full agreement with this statement.

Clarke, in a comparative study based on the rate of slowing caused by digitalis, showed that an effect was evident within three to four hours after intravenous administration, in about four hours after intramuscular administration, and in about six hours after oral administration.

There is no reliable evidence that proprietary preparations of digitalis have any advantage over official preparations.

The use of compound tablets containing digitalis in combination with other drugs is to be condemned, as analysis of their constituents so often reveals the presence of these drugs in such ridiculously small amounts as to be pharmacologically inactive.

Studies dealing with the absorption of digitalis from the alimentary tract of man have been carried on by several investigators. It has been shown that the galenical preparations of digitalis are absorbed with sufficient uniformity to allow the establishment of an average, total therapeutic requirement of the drug, even for samples from various sources and of different activity. Eggleston and Wyckoff showed that a satisfactory, average total dose, expressed in terms of the "cat-unit" of activity for each pound of the patient's weight, was possible when high-grade tinctures were used. The absorption of average tinctures was variable. High-grade tinctures, in sufficiently large doses, revealed definite action on the heart of man within two to four hours after oral administration. Tinctures of less activity required five or more hours for their effects to become manifest.

It must be clearly understood that the first evidence of the action of digitalis does not imply the full therapeutic effect, as this is rarely obtained in less than twenty-four or forty-eight hours, and then only when larger doses are employed.

In the administration of digitalis the difficulty encountered at times in establishing a method whereby the patient is sufficiently held under the action of the drug without eliciting the toxic symptoms of overdosage is well known. The rate of elimination from the body or the degree of destruction in the body have been unknown quantities.

Pardee, in studying the rate of disappearance of digitalis from the body, found that approximately 0.1 to 0.2 gm. is lost in twenty-four hours. These results would imply that at least 0.15 gm. (1.5 c.c.) would be the required daily dose necessary to maintain a digitalis effect after the full therapeutic effect had been obtained.

The establishment of the diagnosis of heart disease is frequently considered the indication for the administration of digitalis. Such a criterion is absolutely fallacious and frequently results in serious difficulty. No method of treatment is attended by greater hazards than the indiscriminate and improper administration of digitalis.

The two striking indications for the employment of digitalis are the presence of congestive heart failure and the presence of auricular fibrillation with rapid ventricular rate. This statement requires modification, as at times in rapid auricular fibrillation the administration of the drug must be cautious or, perhaps, it must be withheld. As previously stated, the establishment of a definite diagnosis of the type of lesion is of primary importance.

The exhibition of digitalis, in cases of acute heart failure, before the exact cause for the failure is determined is not without danger. Heart block, sudden failure from coronary occlusion, and intense hyperthyroidism, especially if crisis is present or impending, are clear-cut contraindications to its use.

The presence of auricular flutter invariably demands medication with digitalis, and often very large doses and prolonged periods of administration are necessary and are well tolerated. These observations suggest that the elimination of digitalis in flutter is perhaps more rapid than in other disorders of cardiac action.

In general, although this statement is not without exception, digitalis is more effective for young and middle-aged patients, especially those with the heart failure of valvular disease, than for older patients with hypertensive, coronary, or syphilitic cardiovascular disease.

There is no doubt that digitalis may be of benefit in cases of failure when the cardiac rhythm is regular. This fact was emphasized by Christian and I believe has been the experience of all who have used digitalis.

My experience with digitalis has led me to be cautious in its administration to older patients, and has led me to give moderate doses over periods that have not been too prolonged.

One of the signs of excessive administration of digitalis is the appearance of premature contractions or extrasystoles. When caused by digitalis, they usually occur paired with the normal beats and result in the so-called coupled rhythm. The presence of premature contractions, however, occurring in a case in which the patient has not received digitalis recently must not be considered as a contraindication for the exhibition of this drug.

Digitalis has little or no value in paroxysmal tachycardia.

The preoperative digitalization of patients with cardiac disease is to be condemned as a routine practice. Several objections to this become evident at once. In the majority of instances, the preoperative administration of digitalis is unnecessary and involves, therefore, an unnecessary loss of time for the patient, with the attendant financial burden. As previously stated, many older patients do not tolerate digitalis well, and if it is indiscriminately given, they may be in a less favorable condition to meet operation. If it is recalled that little can be anticipated from the exhibition of digitalis except in cases in which heart failure is present or has recently been present, the chief contraindication to this procedure becomes evident. If heart failure exists, operative intervention is positively contraindicated, and then only after cardiac function has been re-established by proper treatment.

It is my belief, therefore, that the indications for the routine preoperative digitalization of patients with heart disease lack scientific and clinical confirmation, and that this routine should be discouraged.

Likewise, the routine administration of the drug in cases of pneumonia is not to be encouraged. Controlled studies have failed to demonstrate any justification for continuance of the procedure. When heart disease and pneumonia coexist, and the situation is such that under ordinary circumstances the heart would demand digitalis, or the additional load imposed by pneumonia threatens heart failure, it should be employed intelligently. We must not lose sight of the fact that the patient with pneumonia may be extremely toxic, and that the addition of a toxic drug in a full therapeutic dose may lead to disaster.

As previously stated, the oral method of administration of digitalis is the one of choice. Many patients have failed to receive benefit because too little digitalis has been given; less frequently, harm has resulted from its administration in excessively large doses.

Eggleston demonstrated the possibility of giving relatively large doses of the drug, and his method of administration is known as the Eggleston method. The strength of the preparation employed is determined in cat units, and from this the dose is calculated for man. When the standardized tincture is used, the average requirement in oral administration for production



of the full therapeutic effect or minor toxic action is about 0.146 c.c. for each pound of the patient's weight. For example, a patient weighing 150 pounds (68.1 kg.) would require 21.9 c.c. of the tincture. The calculated total dose is given in divided portions: the first dose is half the total dose; the second, which is given six hours later, is half the remainder, and the third and fourth doses, given at intervals of six hours, are half the second dose.

Eggleston's method has been modified in numerous ways, although the general principle of the method has been maintained.

These methods of administering relatively large doses of digitalis over short periods are not without objection. Their justification implies that the patient has been carefully examined and that the cause of heart failure has been fully determined. After the total calculated dose has been given, means do not exist whereby the action of the drug may be modified, and notwithstanding various opinions the onset of toxic symptoms is highly undesirable, and at times, hazardous.

In the majority of cases of cardiac disease in which digitalis is indicated, sufficient time may safely be consumed to administer smaller individual doses over a longer period of time. Experimental studies have shown that full therapeutic effects, without toxic symptoms, can be obtained with standard preparations in doses of 1.5 gm. (22 grains) of the leaf, or 15 c.c. (225 minims) of the tincture. These therapeutic effects may be obtained even if digitalis has been employed in the same case; however, at least two weeks without digitalis must be allowed to elapse between the two periods of administration of the drug. The administration of 1 to 1½ grains of the leaf or 1.5 to 2 c.c. of the tincture three times daily is a satisfactory and safe method in most cases.

After the development of the therapeutic effect, the problem of maintaining the action of digitalis without the onset of toxic phenomena presents itself. Numerous methods of administering the drug have been employed, but in general two plans are adopted. Digitalis may be given daily, in doses sufficiently large to maintain its effect over relatively long periods of time; or larger doses may be employed, and may be given for a few consecutive days each week with regular periods of withdrawal.

In order to obtain satisfactory results, the method of administration must be selected to meet the needs of the individual case. In my experience, the second method has proved satisfactory. The individual dose, administered three times daily for the necessary number of consecutive days each week, is readily adapted to varying conditions.

The daily administration of ridiculously small doses of digitalis is without scientific support and should not receive encouragement.

It is important to emphasize the great discrepancies in dosage that may occur from the use of ordinary medicine droppers. This unreliable method is to be condemned, as it has been a significant factor in the inadequate administration of digitalis. Some physicians have presumed that a minim of the tincture of digitalis, as measured in a calibrated vial, corresponds to a drop as delivered by the average medicine dropper. That this method is unreliable can be proved by anyone by filling a calibrated vial to a given capacity in minims, using several droppers. Discrepancies of from five to fifteen drops will be observed. The position in which the dropper is held, vertically, obliquely, or horizontally, also results in a discrepancy. Graduated vials are readily available and one should be prescribed with the digitalis; it is easy to instruct the patient in its use.

Under certain conditions digitalis may be given satisfactorily by rectum. This method of administration is particularly applicable if nausea and vomiting are present from other causes. Essentially the same dosage used in oral methods may be used. In order to simplify this procedure, the total daily dose may be given at one time, with 20 to 25 c.c. of water added.

The intravenous and intramuscular injection of digitalis has already been discussed, and I wish to emphasize that the indications for this mode of administration occur only occasionally.

#### TOXIC EFFECTS

Every physician should understand the toxic effects of digitalis. Certain symptoms of overdosage are well known; namely, anorexia, nausea, vomiting, and diarrhea. The occurrence of coupled beats as toxic manifestations has also received con-

siderable emphasis, and likewise the occurrence of partial or complete heart block. Other toxic effects are not so well known and merit considerable emphasis, owing to the fact that they often occur independent of such well-known symptoms as nausea and vomiting.

Occasionally, during the administration of digitalis, paroxysms of tachycardia occur which have been known to terminate in death. The paroxysms have been identified as arising in the ventricles. The occurrence of these phenomena during the course of administration of digitalis in a case in which the patient was not hitherto subject to them, indicates a profoundly toxic effect of the drug.

The toxic effects of digitalis on the brain and certain nervous tissues are important to recognize, as the continued administration of the drug when toxic effects are present, often results fatally. Prominent among these are disturbances in vision. They consist of dimness of vision, inability to focus the eyes, difficulty in identifying objects, and the presence of scotoma, diplopia, and so forth. Yellow and green vision are striking, and are often alarming manifestations of intoxication with digitalis.

Toxic cerebral effects of digitalis are not as yet fully appreciated and are of the utmost importance owing to their seriousness. In older medical writings, allusions are found to the so-called cardiac psychoses, some instances of which were probably the result of intoxication with digitalis. The first symptoms usually are restlessness and increased nervous irritability; periods of disorientation regarding time and place soon follow. These manifestations are frequently supplanted by stupor, from which the patient does not recover. Visual disturbances may or may not be associated phenomena. Toxic cerebral symptoms may occur without the more usual signs of poisoning by digitalis. The onset of any of these symptoms clearly indicates immediate discontinuance of the drug, for the time at least, and the prompt clearance of the tissues; this may at times be possible by the daily intravenous administration of hypertonic glucose solution.



## TREATMENT OF NEPHRITIS

EDWIN G. BANNICK

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WITHIN the past twenty-two years there have been distinct advances in the classification and treatment of nephritis. In 1914, Volhard and Fahr assembled the known clinical, laboratory, and pathologic data and reclassified the various types of nephritis. Since then there have been numerous other similar classifications subdividing the old acute nephritis, chronic parenchymatous nephritis, and chronic interstitial nephritis into smaller groups. There have been many arguments concerning the pathologic changes in the various forms. New terminology such as nephrosis has appeared. Much has been written about hypoproteinemia and a decrease in the osmotic pressure of the serum as important factors in the production of edema. Frequent reference has been made to hypercholesterolemia, inversion of the albumin-globulin ratio in the serum, and decreased basal metabolism. Many articles have dealt with various phases of hypertension. Numerous diuretics have been made available. All of these have resulted in increased knowledge of the pathologic changes, the prognosis, and the treatment of the different types of nephritis, but unfortunately they also have caused some confusion in the minds of many physicians, particularly those who are not specializing in this field, who may feel that the problem is too complicated for the average physician to handle, especially if he does not have ready access to numerous laboratory procedures. I am firmly convinced, however, that this is not correct. Undoubtedly, some special data are at times of distinct value in accurate diagnosis and prognosis, and yet from the practical standpoint most patients who have nephritis can be well treated by any physician who will avail himself of the measures at his disposal and who is familiar with the general principles underlying the present treatment of renal disease. I, therefore, will outline

these general principles and mention the therapeutic measures which I think should receive consideration.

The classification in the Tabulation is a practical clinical arrangement which I have found very useful in the treatment of nephritis.

## TABULATION

### CLINICAL CLASSIFICATION OF NEPHRITIS

#### I. Acute nephritis (old classification: also acute nephritis):

(A) Acute diffuse glomerular nephritis.

(B) Acute nephrosis.

1. Acute chemical nephrosis.

2. Acute toxic nephrosis.

#### II. Chronic nephritis:

(A) Chronic nephritis with edema (old classification: chronic parenchymatous nephritis):

1. With little or no retention of nitrogen:

a. Lipoid nephrosis.

b. Mixed nephrosis.

2. With retention of nitrogen (chronic glomerular nephritis).

(B) Chronic nephritis without edema but with retention of nitrogen (old classification: chronic interstitial nephritis):

1. Chronic glomerular nephritis.

2. Arteriosclerotic nephritis.

### ACUTE NEPHRITIS

It is essential to differentiate the two forms of acute nephritis referred to in the Tabulation. This is advisable both from the standpoint of treatment and prognosis, and it is not difficult to do in most instances.

**Acute Diffuse Glomerular Nephritis.**—This type of nephritis is characterized by hematuria, albuminuria, and usually by some edema, hypertension, or retention of nitrogen, or all of them. In other words, it is a diffuse disease and not one that is limited to the kidneys. The onset is usually abrupt and is often preceded by some demonstrable etiologic factor, such as acute tonsillitis or some type of streptococcus infection. It is true that in some instances edema, hypertension or even the evidence of retention of nitrogen may not be very striking but careful examination and observation should reveal the presence of one or more of them. This finding together with a significant

hematuria and albuminuria is sufficient to establish the diagnosis.

I shall consider treatment somewhat in the form of an outline in order to compare it with the treatment of the other forms of nephritis which are to be described.

*General Measures.*—The patient should be put to bed and kept warm. It is oftentimes advisable to use light flannel garments for this purpose. The length of time that the patient should be kept in bed is rather disputable, but in general the tendency has been to allow these patients to get up much too soon. The patient and the relative must be given to understand that this disease, if properly handled in the early stages, is curable in the majority of instances but that, if allowed to become chronic, it is incurable and ultimately fatal. It would, of course, be desirable to keep such a patient in bed and warm until no abnormalities could be noted in the urine, blood pressure, or renal function, but this is at times impractical and perhaps often unnecessary. The patient should, however, be kept in bed until the edema has disappeared, until the blood pressure is normal, until the free output of urine is established, until hematuria has subsided or markedly diminished, or until there is unmistakable evidence that the disease has changed into the chronic stage. When the patient is finally allowed to get up, precaution should be taken to see that he is kept warm and that his activities are increased very slowly and cautiously. I have seen numerous cases of acute nephritis in which the patients made a splendid temporary recovery but the disease became chronic because the patient engaged in active work, oftentimes heavy farm work which was associated with chilling and exposure. In the early stages it is advisable to keep the bowels open by the use of mild laxatives, but I have not been impressed with the value of any purging, and this has been the experience of numerous other physicians.

*Diet.*—In the cases of mild nephritis, little dietary restriction is necessary. The diet should be adequate in amount and variety with only a little reduction in the protein content; many physicians do not even advise the latter. If edema is present, intake of salt should be reduced. A normal amount of fluid should be allowed unless there is considerable edema, when some restriction of fluids is desirable. In cases of severe

acute nephritis the immediate objective of the diet should be to put the kidney at rest as much as possible. Volhard, in Germany, usually gives the patient nothing by mouth for from three to five days, and Ellis, of England, gives only a pint of orange juice daily for ten to fourteen days. I have not deemed it necessary to restrict the patient as much as this, but I agree with the general principle of food and fluid starvation in the early stages of severe nephritis. I have usually prescribed only small amounts of fruit or fruit juices by mouth for the first few days and then have gradually increased the diet, but the protein content is kept low (around 30 gm. daily), the salt is restricted, and the diet, of course, is kept free from condiments, extracts, and irritants of all kinds. After a couple of weeks the protein content and the caloric value of the diet should be increased until the patient is taking an adequate diet with only moderate restriction of protein and salt.

*Fluids.*—In cases of severe nephritis the ingestion of fluids should be markedly limited for the first few days for the same reason that the diet is restricted. After a few days, however, the fluids should be gradually increased, depending on the degree of oliguria and the amount of edema that are present. There has been a general tendency to give too much fluid in the early stages of this disease. I do not advise giving more than 2,500 c.c. of fluid during twenty-four hours, and this quantity should be given only later when the patient is excreting a considerable amount of urine and when there is no edema. It seems reasonable that if the patient is receiving 2,500 to 3,000 c.c. of fluid daily and is excreting only 200 to 300 c.c. of urine daily, without any excessive loss of fluid through the other channels, an unfavorable situation will result. Under these circumstances, I think the amount of fluid should be reduced again. I have seen numerous instances in which such a fluid imbalance has been allowed to persist for a considerable length of time without any demonstrable peripheral edema, and yet at necropsy the patient was found to be markedly water-logged. In case the oliguria persists, it is advisable to give some of the fluids intravenously in the form of hypertonic solutions. It is advisable to begin by using a 10 to 20 per cent solution of dextrose. If the oliguria is marked, 500 c.c. of a 20 per cent solution of dextrose should



be given intravenously. If it is not marked, 750 c.c. or even 1,000 c.c. of a 10 per cent solution of dextrose may be used instead. In some cases in which the condition is obstinate, sucrose has seemed to produce even better results, because the diuretic effect of the hypertonic solution of sucrose is maintained much longer than that of dextrose, inasmuch as sucrose is not utilized by the body as is dextrose, and must be largely excreted through the kidneys. The solution of sucrose must be carefully prepared, however, and in cases in which this has been done, I have not had any unsatisfactory experiences with it either in the way of toxic reaction or renal damage. If there is persistent oliguria and considerable retention of nitrogen, there is usually an associated acidosis, in which case it also is advisable to administer 300 to 500 c.c. of 5 per cent solution of bicarbonate of soda intravenously.

*Diuretics.*—Apart from the intravenous administration of the hypertonic solutions which have been mentioned, diuretics are for the most part not indicated. I do not believe that other diuretics are of much value unless there is considerable edema, and this is not true in the vast majority of cases in which the treatment is well managed. The field for diuretics is in cases in which there is edema and not in those in which there is acute oliguria. The administration of salyrgan, a compound of organic mercury, is distinctly contraindicated and would likely produce further damage if used, and I have noted little value from the acid-producing salts (ammonium nitrate, ammonium chloride, and calcium chloride) or from potassium nitrate, or the definitely alkaline diuretics, and if any of these are not very carefully administered, toxic symptoms will result in cases in which there is oliguria. The use of the xanthine diuretics in these cases also has resulted in considerable controversy. It has been argued that they are renal irritants and, therefore are likely to result in further damage to the kidneys. I have not been particularly impressed with this fact myself and as a result of this have used some of the xanthine diuretics in some instances of oliguria in acute glomerular nephritis, but I have not been much impressed with the benefits obtained. In some cases where there is considerable hypertension with evidence of myocardial insufficiency, administration of digitalis may produce much benefit.

*Special Symptoms.*—The special symptoms that require further consideration are anuria and convulsions. Anuria is fortunately rare, but when it occurs it presents a very serious and difficult therapeutic problem. Of course, it is advisable first to catheterize the patient to be sure that anuria actually exists. Then, it is advisable to administer some hypertonic solution intravenously, as previously mentioned, that is, 500 c.c. of a 20 per cent solution of dextrose, 350 c.c. of a 30 per cent solution of dextrose, or 400 to 500 c.c. of a 25 per cent solution of sucrose. It is often advisable to precede the intravenous injection of the fluid with a venesection and the withdrawal of 400 to 500 c.c. of blood. This is particularly true in cases in which there is acute hypertension. Intravenous administration of a 5 per cent solution of sodium bicarbonate is advisable if the anuria persists. Surgical decapsulation of one or both kidneys should, of course, receive serious consideration in the face of persistent anuria. However, the selection of suitable patients for this operation is very difficult. If one can be sure that he is dealing with an acutely swollen kidney, and if the conservative measures which have been outlined have failed to produce satisfactory results, and if the patient is steadily losing ground, this surgical procedure should be instituted before the patient's condition becomes hopeless. This procedure has unquestionably resulted in the recovery of patients who otherwise would certainly have died. It should be borne in mind, however, that many times, when the surgeon was about to perform such an operation and before it was done, spontaneous diuresis has occurred. In many other instances the patients have been poorly selected so that the kidney was not found to be acutely swollen and tense, and no benefit has resulted from the decapsulation. Diathermy and very light doses of roentgen rays over the kidneys have been recommended, but I have failed to see any significant benefit in the few cases in which I have tried these measures.

In my experience convulsions are not common during acute nephritis which affects adults. Several measures must be considered in the treatment of convulsions when they do occur. First of all, it is advisable to see that the patient is propped up in bed with his head well elevated. This is particularly true if considerable edema is present. Sedative drugs, such as

chloral hydrate or the barbiturates, are, of course, indicated. The latter drug is given subcutaneously or even intravenously in certain instances. Venesection followed by the intravenous injection of a hypertonic solution of dextrose is often beneficial. In these instances I prefer the intravenous administration of small amounts of a strongly hypertonic solution of dextrose, for example, 250 to 300 c.c. of a 25 or 30 per cent solution, after the withdrawal of 400 to 500 c.c. of blood. I have seen lumbar puncture with the withdrawal of some cerebrospinal fluid stop a series of convulsions in several instances, and peculiarly enough, it may do so even when the cerebrospinal fluid is under no demonstrable increased pressure. Magnesium sulfate administered intramuscularly has been used with benefit by some physicians, but I have not had occasion to use it. The dose recommended is 0.2 to 0.4 c.c. of a 25 per cent solution for every kilogram of body weight. This may be repeated in two to three hours if necessary.

*Removal of Foci of Infection.*—Lastly in the management of acute diffuse glomerular nephritis, the problem of removal of foci of infection must be considered. Definite foci of infection should be eradicated. In the past it has been the policy to postpone removal of the focus until the attack of nephritis was well under control and until the hematuria and albuminuria had markedly diminished, but more recently there has been a feeling among many physicians working in this field that early removal of significant foci is desirable. A few years ago I discussed this problem at some length with Professor Nonnenbruch, of Prague, who has had a large experience in the management of renal disease, and he was convinced that prompt removal of significant foci in such cases was not dangerous but distinctly advisable. At the clinic we have removed foci of infection somewhat earlier than formerly, and yet we still prefer to remove them after the acute process has largely subsided unless the focus shows a very active infection and the hematuria is profuse, in which case early removal of the focus is indicated. In cases of very mild nephritis in which there are no abnormal findings except albuminuria and hematuria, prompt removal of significant foci of infection frequently results in a rapid cure without the necessity of much

else in the way of treatment, but subsequent close rechecking of such cases is advisable.

**Acute Nephrosis.**—Two types of this form of nephritis can be distinguished according to the etiology, namely, acute chemical nephrosis and acute toxic nephrosis.

*Acute Chemical Nephrosis.*—The most frequent cause of this condition is ingestion of bichloride of mercury. Other poisons which can produce it are uranium salts, chromium salts, arsenic, tartrates, phenol, and fluorides. The clinical picture is that of azotemia and oliguria which may become an actual anuria. The small amount of urine may contain albumin, blood, and casts as a result of the tubular necrosis. Edema and hypertension are rare except as late phenomena in cases in which the condition is poorly managed or proves fatal.

The therapeutic indications are chiefly twofold: (1) the prompt removal of as much as possible of the poison from the gastro-intestinal tract and neutralization of the remainder by proper antidote when possible, and (2) the treatment of the acute anuria, which has been described in the treatment of anuria in the preceding pages. Of importance in the treatment of poisoning with bichloride of mercury is the announcement by Rosenthal of an effective antidote for this substance. The antidote is sodium formaldehyde sulfoxylate (a powerful reducing agent) which reduces the toxic preparations of mercury to the mercurous state and to metallic mercury. The patient's stomach should be washed promptly and 200 c.c. of a 5 per cent solution of this antidote should be left in the stomach. This may be followed by the intravenous injection of 10 gm. of this preparation in 100 to 200 c.c. of distilled water. This may be repeated if the condition is severe. This treatment is highly effective as late as two hours after the ingestion of the poison and should be tried even if a longer period has elapsed.

*Acute Toxic Nephrosis.*—Whereas acute chemical nephrosis is fortunately rare, acute toxic nephrosis is very common, in fact, this represents one of the most common clinical forms of acute nephrosis or nephritis which the physician is called on to treat. It occurs in the course of many severe types of toxemia, as peritonitis, jaundice, empyema, septicemia, toxic gangrene, intestinal obstruction, pneumonia, malaria. Clinic-

ally, this form of nephritis differs from acute diffuse glomerular nephritis chiefly in the absence of such extrarenal factors as hypertension and edema, although edema may occur later if excessive amounts of fluid and salt are allowed with persistent oliguria. Urinalysis also does not reveal the degree of albuminuria and hematuria commonly seen in cases of acute diffuse glomerular nephritis. In some instances a moderate albuminuria occurs, but hematuria is absent or slight. As in the cases of acute chemical nephrosis, the characteristic clinical findings are oliguria and retention of nitrogen. The severity of the symptoms varies greatly; there may be mild simple febrile albuminuria with good renal function or there may be fatal anuria and uremia. Pathologically, the renal changes also are not consistent. If the underlying etiologic factor can be corrected, the recovery is usually prompt and complete. Acute toxic nephrosis, therefore, may present an entirely different problem from that of acute diffuse glomerular nephritis and does not usually require the rigid management of the latter. The treatment otherwise is similar to that of acute oliguria in the more diffuse form of the disease with the exception that a more liberal fluid intake is advisable. This, however, as in the other group, depends on the degree and persistence of the oliguria. I think it is advisable to give 2,500 to 3,000 c.c. of fluid daily in such cases provided the output of urine increases proportionately, and if it does not, the intake of fluids must be gradually reduced so as to prevent the patient from becoming water-logged. During the period of oliguria it is advisable to restrict the intake of both salt and protein. Diuretics of the xanthine group are often of benefit in these cases. Of this group I prefer to administer theophylline-ethylenediamine (aminophyllin, euphyllin) in doses of 0.2 gm. three to five times daily. If the drug cannot be administered by mouth, it may be given subcutaneously or intravenously.

#### CHRONIC NEPHRITIS

Before taking up the various types of this condition, I would like to emphasize two broad general principles which govern its management. If the physician is thoroughly familiar with these principles, he should be able to prescribe in a

rational manner without necessity of a large amount of laboratory data. These broad general principles as applied to the treatment of chronic nephritis are as follows: (1) edema calls for the use of diuretics, rigid restriction of salt, some restriction of fluids, and of itself does not call for any restriction of protein; (2) retention of nitrogen of itself calls for restriction of protein, no restriction of salt, liberal administration of fluids, and no diuretics.

First, I wish to consider the *cases of chronic nephritis with edema*. This group for therapeutic reasons is divided into those with little or no retention of nitrogen and those with retention of nitrogen. The former includes those rare cases of chronic lipoid nephrosis in which the condition is handled in practically the same manner.

**Chronic Nephritis with Edema Having Little or No Retention of Nitrogen.**—The most progress in the treatment of chronic nephritis in recent years has been made in this group because of the knowledge of the rôle of the decrease in the serum protein in the production of edema and because of numerous suitable diuretics which have been developed. Although Bright himself, in his early writings, was aware of the decrease in the plasma proteins in these cases, for the most part patients who belong to this group have been badly managed for many years. Presenting themselves to the doctor with marked edema and marked albuminuria, the doctor was very likely to prescribe a diet rigidly restricted in protein because they had Bright's disease, and the doctor had been taught that patients who had Bright's disease should have very little protein. Epstein's contributions, based on Starling's earlier observation (1895-1896), opened up a new field of thought in the management of these patients. Starling showed that it is presumably the osmotic attraction of the plasma proteins for water that balances in the capillaries the hydraulic pressure tending to force the fluid out into the tissue spaces, and that when the protein osmotic pressure weakens, because of decrease in concentration of protein, undue amounts of fluid are likely to pass out into the tissues. Epstein (1917) made clinical application of Starling's experimental and theoretical work by observing a marked deficit in plasma protein in cases of chronic nephrosis in which there was noncardiac edema. These

observations have since been confirmed by many workers. He found further that the serum albumin was diminished chiefly and that there was, therefore, a tendency to inversion of the normal albumin-globulin ratio with still further decrease in the serum osmotic pressure. Govaerts (1924) showed that the albumin exerts four times as much osmotic pressure per gram as does the globulin. Epstein postulated that the decrease in the serum protein was attributable to loss of huge amounts of albumin through the kidney and, therefore, in place of a restricted protein diet which would further increase the serum protein deficiency, the patient should have a very high protein diet.

Time has shown that the hypoproteinemia is not entirely attributable to loss of albumin through the kidneys and that the value for the serum protein is not easily or uniformly elevated simply by the ingestion of an excess of protein. The ability of the patient to metabolize and utilize the protein given is, of course, a very important factor and experience has taught us that very high protein diets are unnecessary and may actually be harmful in some instances. On the other hand, since in these cases there is little tendency to retention of the end-products of protein metabolism and since the values for the serum protein are consistently low and there is considerable loss of albumin in the urine, the protein should not be restricted. The diet, therefore, should contain ample protein to insure a positive nitrogen balance with an additional supply available for storage. Approximately 100 gm. daily seems to be adequate for the average adult, and this amount is usually well tolerated by the patient. A rigid restriction of salt is also very important in controlling the edema.

The influence of a rigid restriction of salt on nephritic edema has been known for a long time, and further comment is unnecessary except to emphasize this fact and to point out that the food must be carefully prepared without the addition of any salt if the best results are to be obtained, and the butter must be free of salt. Fluid should be moderately but not rigidly restricted. Some physicians, notably Lashmet and Newburgh, at the University of Michigan, expressed the opinion that liberal amounts of fluid should be given and that if the salt is markedly restricted this will result in increased

elimination of salt and with it water. My experience has been that the edema is more easily controlled with moderate restriction of water in addition to rigid restriction of salt.

*Diuretics.*—Diuretics are usually indicated, in fact, this group of patients presents the chief field for the use of diuretics in nephritis, and numerous ones are available. At the clinic, we prefer the acid-producing salts (ammonium chloride and ammonium nitrate) or potassium nitrate and potassium chloride, which produce a mildly alkaline reaction. The nitrate salt in each group is the more effective diuretic. These salts will cause an increased elimination of salt and water in most instances. They are given by mouth in doses of from 8 to 12 gm. daily (ammonium nitrate usually is given in doses of 8 to 10 gm. daily, and potassium nitrate in doses of 10 to 12 gm. daily) and can be administered over a prolonged period with benefit and with safety if the patient is closely observed. Since the ammonium salts cause an increase of urea and a decrease in the alkali reserve, determinations of the blood urea and the carbon dioxide combining power of the plasma should be made periodically during their administration. Potassium nitrate is less likely to cause significant changes in the chemistry of the blood, and since it is a more efficient diuretic we are using it chiefly at the present time at the clinic. These drugs can be obtained in 0.5 gm. enteric-coated pills and if so administered do not as a rule cause nausea or vomiting.

Definitely alkaline diuretics have also been used successfully, particularly by English physicians, but the dosage in order to be effective must be large, and the potassium salts rather than the sodium salts are preferable because they produce better diuresis.

Bennett suggested the following:

Potassium bicarbonate	..	15 grains (1 gm.)
Potassium citrate		15 grains (1 gm.)
Water to make 1 ounce	(30 c.c.)	

An ounce of this to be taken every six hours, every four hours and every two hours, respectively, on successive days until the urine is fully alkaline.

Osman used considerably larger doses of a mixture of



potassium citrate, potassium bicarbonate, sodium citrate, and sodium bicarbonate in equal amounts. Such large doses of alkalis are often difficult to administer because of the tendency toward vomiting and diarrhea, and tetany constitutes one of the menaces of this treatment. Thus, it is interesting to note that diuresis may occur either following the use of large doses of alkalis or following the use of acid-forming salts such as I have mentioned, or following the administration of the very mildly alkaline potassium nitrate, and this fact should be kept in mind in managing obstinate nephritic edema. At the Clinic, we prefer ammonium nitrate or potassium nitrate because diuresis is more prompt, more striking and more constant, and the administration of the drugs is more simple and better tolerated by the patient. Urea is also used as a diuretic, but I believe that the ammonium salts described previously are much more efficient and may be used in any case in which the administration of urea is indicated. If there is evidence of complicating myocardial failure, the use of digitalis should be considered. In certain selected cases of chronic nephritis with edema and without nitrogen retention, the organic compound of mercury salyrgan has been used in conjunction with the acid-producing salts or potassium nitrate with good results, particularly in cases of chronic lipoid nephrosis, but this compound should be cautiously administered at all times, and if there is hematuria it should not be used. Much harm can result from the indiscriminate use of this potent diuretic drug whose chief field of usefulness is after all in the treatment of cardiac dropsy rather than in the treatment of nephritic edema. In obstinate nephritic edema without hematuria, it may prove to be very effective and probably without danger if properly administered. The initial dose should not exceed 0.5 c.c. intravenously, and if no untoward effects result from this the dose may be increased to 1 or 2 c.c. given not oftener than every four days and preferably at longer intervals. Other diuretic substances such as thyroid extract and the xanthine compounds should be kept in mind but have rarely been necessary nor very effective in my experience in this type of case.

Other measures, in addition to a liberal protein diet, have been advocated to aid in elevating the value for the plasma protein and the osmotic pressure of the serum. Blood trans-

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fusions are of undoubted value in doing this and would be used oftener for this purpose were it not for the fact that they are expensive and usually are not necessary. Intravenous injections of solutions of acacia have been used to increase the osmotic pressure of the serum. To be effective large doses must be given and may have to be repeated. The results have been variable and this method of treatment has not received general acceptance.

All definite foci of infection should be eradicated if the patient's condition and his ultimate life expectancy warrant it. This is particularly true in the cases of lipoid nephrosis in which the prognosis is good and in which recurrences of edema are common, but good judgment must be used because a severe exacerbation of the disease may be produced by the untimely removal of foci. A warm, dry, equable climate is preferable if economically possible, as it is in all cases of nephritis.

**Chronic Nephritis with Edema and Retention of Nitrogen.**—This group presents a hard therapeutic problem because of the difficulty of planning a diet to combat both the edema and the azotemia, and because few suitable diuretics are available. The *diet*, of course, should be as free of salt as possible, just as it should be in the cases of edema without retention of nitrogen, but the amount of protein in the diet should be moderately reduced. However, because of the edema and the decreased value for the plasma proteins and because of the albuminuria, it is not wise to restrict the proteins in the diet rigidly. Sufficient protein should be allowed to maintain a positive nitrogen balance. A diet containing from 50 to 60 gm. of protein is usually sufficient to do this. This may need to be altered somewhat as treatment continues, depending on whether azotemia becomes the prominent symptom, in which case further slight reduction in the amount of protein may be made, or whether edema becomes the prominent symptom, in which case a more liberal amount of protein may be allowed. A fairly liberal fluid intake should be allowed, at least until the azotemia has been reasonably well controlled. It is often advisable to administer some of the fluid (500 c.c.) intravenously in the form of 20 per cent solution of dextrose or a 25 per cent solution of sucrose, because of the diuretic properties of such hypertonic solutions.

Suitable *diuretics* are somewhat limited. The organic compound of mercury (salyrgan) is usually contraindicated because of the likelihood of causing further renal damage. Ammonium chloride and ammonium nitrate tend to produce further retention of nitrogen and acidosis, and, therefore, are usually not desirable. Potassium nitrate is somewhat safer and more effective, but it must also be used cautiously, in smaller doses, and over a shorter period than usual because of the danger of a toxic reaction from the retention of potassium. It should not be used at all if the value for the blood urea is as high as 100 mg. per 100 c.c. The same caution must be used in administering potassium citrate or potassium bicarbonate. The alkaline diuretics, sodium bicarbonate and sodium citrate, and the xanthine diuretics, particularly theophylline-ethylenediamine (aminophyllin, euphyllin) or theobromine calcium salicylate (theocalcin) may be tried. These have been referred to in the previous pages, but, as mentioned, they have not in my experience produced uniform effective diuresis. Blood transfusions may be of much benefit in treating the edema, the anemia, and the azotemia.

**Chronic Nephritis without Edema but with Retention of Nitrogen.**—As mentioned previously under the general principles in the treatment of chronic nephritis, the ingestion of protein should be restricted in this type of nephritis, salt should not be restricted, and a liberal fluid intake should be allowed. In such cases the nephritis is unfortunately frequently overlooked and a liberal amount of protein is allowed because the most prominent presenting symptom is often anemia, for which treatment is given. If such a patient is thoroughly examined, hypertension and low specific gravity of the urine with some degree of albuminuria or hematuria practically always will be noted, in which case the azotemia should be suspected and easily proved, and proper treatment instituted. It has been aptly said that the combination of anemia and hypertension should make the physician suspect, first of all, chronic nephritis. It is not advisable to reduce the daily intake of protein below 40 gm. Further restriction than this over a prolonged period is likely to result in utilization of the protein in the patient's tissues. If the patient understands

that the average normal diet contains approximately 70 to 90 gm. of protein, he can readily appreciate to what extent he should reduce the protein in his own diet, even if no actual dietary list is given to him. A normal amount of salt is allowed because there is no edema, and the value for the plasma chloride is usually reduced. A liberal fluid intake of from 2,500 to 3,000 c.c. daily is advisable unless there is associated threatening cardiac decompensation. The fluid may be given orally unless prevented by nausea or vomiting, in which case some of it may be given rectally, subcutaneously, or intravenously. If the last method is used, a physiologic solution of sodium chloride or a 5 per cent solution of dextrose is preferable and should be slowly administered so as not to cause cardiac embarrassment. Diuretics other than the fluids which have been mentioned are of little value and, with the exception of digitalis, are not indicated in cases in which associated cardiac decompensation is present. Blood transfusions may have a temporary beneficial effect on the anemia and the azotemia if the economic status justifies such therapy. The anemia is very resistant to treatment. I have tried iron, bone marrow extract, and liver extract without any significant beneficial results.

The hypertension of chronic nephritis demands no particular therapeutic consideration, and when renal insufficiency exists, attempts to lower the blood pressure are inadvisable. Fortunately, however, they are usually unsuccessful. Cardiac failure is always threatening in the late stages of the disease, and the cardiac load should be reduced as much as possible. Digitalis may be beneficial in bolstering up the heart before actual decompensation occurs.

## SIGNIFICANCE OF HEMATURIA

JOHN L. EMMETT

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A TREMENDOUS amount of statistical data has been accumulated on the subject of hematuria. In fact, so much information on this subject is available that the presence of hematuria at once stipulates that certain probabilities exist with almost mathematical certainty. The statistics furnished by Lower, MacKenzie, Van Duzen, Kretschmer, and Debenham speak for themselves. Large masses of detailed figures are often soon forgotten and the average practicing physician finds it difficult to keep abreast of the current medical literature, let alone find time to go to a well-stocked medical library and delve into articles of the past. For this reason, an occasional brief résumé of such an important subject in the current journals is valuable.

Articles on the subject of hematuria usually begin with a scathing criticism of physicians who neglect to investigate every case of hematuria thoroughly. Almost every article ends with a plea to the profession to stop prescribing medication for hematuria, but instead to urge the patient to submit to a thorough urologic examination. Personally, I believe that an extremely large proportion of the medical profession is alert to this subject. Patients who have extensive advanced lesions of the genito-urinary tract occasionally have been treated with drugs for months or years, but if the true facts were known it would be found only too often that the patients probably had refused the advice of their physicians and had insisted that symptomatic treatment be given.

There is another very important phase of this subject that is frequently forgotten. The specialist in a large clinical center who sees a tremendous number of referred patients becomes so overly aware of certain disease conditions that he often criticizes

too severely the physician who occasionally misses a diagnosis. One must remember, for instance, that the general practitioner in a relatively small community who does not have ready access to a roentgenologic laboratory is not able to subject every patient who has gastric distress to a thorough roentgenologic study of the gastro-intestinal tract. The clinical acumen which he has gained from years of hard-earned experience should enable him to select the patients who should be sent for complete investigation. It is only in this way that the medical expense of the community can be kept within reason.

The problem of the practitioner therefore is to follow a course that will supply the highest type of scientific diagnosis to his clientele with the minimum of diagnostic errors as well as the minimum of unnecessary expensive special examinations. With this truism in mind, I shall consider hematuria from the *practical standpoint of the general practitioner*.

The term "hematuria" means blood in the urine; the blood may be seen either grossly with the naked eye or with the microscope. Should the microscopic appearance of blood in the urine be regarded with the same suspicion as gross hematuria or may it be disregarded? Is the physician requiring too much of his patient if he insists on a complete urologic examination when only a few erythrocytes have been found in the urine? A practical answer to these questions is that, when the microscopic appearance of blood in the urine is not associated with symptoms, repeated urinalysis should be made. If the erythrocytes persist in the urine or if they appear intermittently, the condition should be regarded with the same suspicion as gross hematuria. It must of course be remembered that it is necessary to obtain a catheterized specimen of urine if the patient is a woman, as erythrocytes in a voided specimen are of no diagnostic significance. The rule may be laid down, therefore, that if microscopic hematuria persists on several subsequent examinations or if it is found intermittently, it must be regarded with the same suspicion as gross hematuria.

In the remainder of the paper I shall speak of hematuria as indicating gross hematuria or persistent or intermittent microscopic hematuria. It is not the purpose of this paper to present imposing complete lists of the conditions, both medical and surgical, in and outside of the genito-urinary tract, that



may be responsible for the hematuria, but rather to acquaint the physician with the serious possibilities involved and suggest a rational and practical plan of procedure.

The problem involved in hematuria becomes apparent when one analyzes the 798 consecutive cases of hematuria reviewed by Lower. In almost a third (32 per cent) of these cases the hematuria was the result of new growths in the genito-urinary tract; in 11 per cent of the cases it was attributable to tuberculosis, and in 16 per cent of the cases it was the result of a calculus. In other words in 59 per cent of the cases the patients were suffering from a most serious condition that demanded early diagnosis if any hope of cure were to be offered. Armed with the facts, therefore, that the chances are about six in ten that one of the preceding conditions might be present, it should not be difficult for the physician to convince patients who are suffering from hematuria that a complete urologic examination is imperative.

There are a few general statements that are easily remembered concerning hematuria. Hematuria is much more common among men than it is among women. The most common cause of hematuria among women is inflammation of the genito-urinary tract, while the most common causes of hematuria among men, in the order of their frequency, are vesical tumors and benign prostatic hypertrophy. Debenham made an interesting investigation of 742 consecutive cases of hematuria. For the sake of analysis these cases may be divided into two groups. Group 1 will be used to include the 510 cases in which the patients were men and group 2 will be used to include the 232 cases in which the patients were women. Inflammation of the genito-urinary tract was the cause of the hematuria in 16 per cent of the cases in group 1 and in 46.5 per cent of the cases in group 2. It is not generally realized that benign prostatic hypertrophy is a much more common cause of hematuria among men than is carcinoma of the prostate gland. In 10 per cent of the cases in group 1 the hematuria was the result of benign hyperplasia of the prostate gland and in 3 per cent of the cases in this group the hematuria was attributable to carcinoma of the prostate gland. In 130 of the cases in group 1, the patients were more than sixty years of age. In 84 per cent of these 130 cases, the hematuria was attributable to carci-

noma of the bladder or prostate gland, benign prostatic hyperplasia, or stricture of the urethra.

A note of warning should be sounded concerning the attempt to determine the source of the hematuria by noting the time of appearance of the blood in relation to the act of micturition. If blood appears at the urethral meatus only between micturitions, the probability is that the source of the bleeding is anterior to the compressor urethrae muscle. However, the fact that the blood is initial, terminal, or completely mixed with the urine should not lead the physician to prognosticate its source. One frequently is led completely astray in this manner. Another point of importance, concerning which the physician must constantly be on the alert, is regarding the women who come to him complaining of irregular menstrual bleeding. Close questioning of such patients will occasionally reveal that their real trouble is hematuria. A carefully taken history in such cases will often avoid serious delay in diagnosis.

As a rule, cases of hematuria may be classified into three groups, according to the etiology. The first group includes cases in which the hematuria is a complication of some systemic disease, such as hemophilia, polycythemia vera, purpura hæmorrhagica (and symptomatic purpura), Hodgkin's disease, scurvy, paroxysmal hematuria, hypertension, various types of nephritis, including the acute nephritis which follows acute infective diseases such as scarlet fever, tonsillitis, and measles. Cases in which hematuria is caused by administration of drugs such as cantharides, turpentine, methenamine, and sodium salicylate, or by the ingestion of foods which are rich in oxalates also belong in this group. Group 2 includes cases in which the hematuria is the result of diseases of organs adjacent to the urinary tract. In these cases, of course, the possibilities are bizarre and unlimited and the condition may be caused by such diseases as carcinoma of adjacent structures, hernia with incarceration of the bladder, and pelvic inflammatory disease. Group 3 consists of cases in which the hematuria is caused by intrinsic lesions of the genito-urinary tract.

A good insight into the average incidence of these various conditions may be obtained by an analysis of the 860 cases of hematuria reviewed by Kretschmer. The causative lesion in these cases is shown in the Tabulation. It is of interest to

note that in 235, or 76.5 per cent, of the 307 cases in which the hematuria was attributable to lesions of the bladder the exciting cause was either carcinoma or papilloma.

The practical approach to the problem of diagnosis is not as formidable as this complete array of possible sources of hematuria would suggest. In fact, the problem may be approached as swiftly and as orderly as a chemical problem in qualitative analysis. For instance, it may be noted in the Tabulation that in 824, or practically 96 per cent of the 860 cases, the hematuria was the result of lesions within the genito-urinary tract, while in nine of the remaining thirty-six cases the hematuria was the result of systemic disease; in twenty-seven cases the cause of the hematuria was not diagnosed. These twenty-seven cases no doubt belong to group 1 or group 2, or were cases of essential hematuria.

The first step one should take, therefore, in all cases of hematuria is to make a complete urologic examination, which should establish the diagnosis in at least 95 per cent of cases. This should be done in spite of the fact that associated conditions such as hypertension or questionable chronic nephritis might possibly be causative agents. The burden of proof rests on the physician, who should make certain that there is not an intrinsic lesion of the genito-urinary tract. With modern urologic methods this is usually easy to do.

After this procedure there will remain only approximately 5 per cent of cases in which the physician will need to look further for the source of the hematuria. It is hardly within the province of the urologist to advise methods of procedure in the latter group of cases. Excellent articles have been written on the diagnosis of these medical conditions and almost every physician is acquainted with this phase of the problem. A word might be said here about the term "essential hematuria." This term has been used to denote those cases in which every effort that has been expended to establish a diagnosis as to the source of the bleeding has been unavailing. Of course this term, like the term "rheumatism," smacks of ignorance. In some of these cases the hematuria no doubt is the result of early lesions of the upper part of the urinary tract that are too small to be demonstrated by retrograde pyelograms or intravenous urography. However, there are cases in which

## TABULATION

## CAUSES OF HEMATURIA IN 860 CASES REVIEWED BY KRETSCHMER

<i>Lesions of the kidney</i>	<i>Cases</i>
Tuberculosis .....	80
Stone .....	71
Pyelitis .....	58
Tumor .....	37
Nephritis .....	31
Pyelonephritis .....	13
Hydronephrosis .....	12
Polycystic disease .....	7
Suspected tuberculosis . . . . .	5
Pyonephrosis .....	4
Syphilis .....	2
Follicular pyelitis .....	1
Infarction .....	1
Movable kidney . . . . .	1
Echinococcus disease . . . . .	1
Pyelitis of pregnancy .....	4
Hematuria of pregnancy . . . . .	2
Total .....	331 (38.4 per cent)

<i>Lesions of the bladder</i>	<i>Cases</i>
Carcinoma . . . . .	163
Papilloma . . . . .	72
Stone . . . . .	31
Tuberculosis . . . . .	14
Cystitis . . . . .	6
Elusive ulcer . . . . .	5
Diverticulum . . . . .	4
Polyps . . . . .	3
Incrusted cystitis . . . . .	3
Ulcer . . . . .	2
Cystitis cystica . . . . .	1
Chronic cystitis caused by ovarian abscess . . . . .	1
Angioma . . . . .	1
Rupture of artery . . . . .	1
Total .....	307 (35.6 per cent)

<i>Lesions of ureter</i>	<i>Cases</i>
Stone . . . . .	48
Stricture . . . . .	5
Carcinoma . . . . .	1
Total .....	54 (6.3 per cent)

<i>Lesions of urethra</i>	<i>Cases</i>
Papilloma .....	2
Stricture .....	2
Prolapse of female urethra .....	1
Polyp .....	1
Total .....	6 (0.7 per cent)
 <i>Lesions of prostate gland</i>	 <i>Cases</i>
Benign hyperplasia .....	64
Carcinoma .....	43
Bar and diverticulum .....	5
Stone .....	4
Bar .....	3
Tuberculosis .....	3
Abscess .....	2
Benign hyperplasia with carcinoma of bladder .....	2
Total .....	126 (14.6 per cent)
 <i>General diseases</i>	 <i>Cases</i>
Purpura .....	4
Cirrhosis of liver .....	2
Hemophilia .....	1
Banti's disease .....	1
Phosphaturia .....	1
Total .....	9 (1.0 per cent)
Source of hematuria not diagnosed .....	27 (3.2 per cent)

patients suffer from intermittent hematuria for years without any impairment of their general health. No cause for the bleeding can be found in these cases. Bumpus reviewed 155 cases of "essential hematuria" five to twenty years after the diagnosis had been made at the Clinic and found that definite renal disease developed in only six of these cases. Calculi developed in three of these cases and in the remaining three cases nephrectomy was performed for unknown reasons. His conclusion was that there are many cases in which kidneys bleed without any demonstrable pathologic change and he expressed the opinion that the term "renal epistaxis" probably described this condition more accurately than any other term. The study of Wilbur and Priestley also substantiates this view. The value of a prompt and early diagnosis is enormous to the patient who is suffering from hematuria. For instance, in

the group of cases in which malignancy of the genito-urinary tract is found (which comprises almost a third of all the cases of hematuria), early diagnosis constitutes the only chance of cure. Braasch and Griffin, and Hand and Broders have emphasized the encouraging results of nephrectomy in the early treatment of malignant tumors of the kidney and ureter by reporting a number of five-year cures. Small early lesions of the bladder are often very satisfactorily cared for, whereas those that have been neglected and have grown to large proportions are absolutely hopeless. It is a regrettable fact, that as noted by Kretschmer, the average length of time, between the first attack of hematuria and the urologic investigation was two and a third years. The Committee on Carcinoma Registry of the American Urological Association found that in 46.45 per cent of cases of carcinoma of the bladder the disease had not been diagnosed one year after the first appearance of the hematuria. It is necessary to strive for earlier diagnosis. In malignant disease and in renal tuberculosis the only hope of cure lies in the early recognition of the condition when there is a possibility that the lesion may still be unilateral and before too much damage has occurred in the bladder. As far as calculous disease is concerned, many kidneys have been completely and painlessly destroyed when they could have been saved by early removal of the obstructing calculus when hematuria was first noted.

Having laid down the dictum, therefore, that every patient suffering from hematuria should be subjected immediately to a complete urologic examination, the economic problem again arises as to the proportion of a community that must be submitted to such inconvenience and expense. Van Duzen, in a review of 21,000 consecutive patients seen in an average clinical practice, found that 500, or only 2.38 per cent presented microscopic or gross evidence of blood in the urine. Eliminating those cases in which the hematuria was probably an accidental finding in the course of microscopic examination and could not be found on repeated examinations, one might estimate that between 1.5 and 2 per cent of patients seen in a general practice will require complete urologic examination because of hematuria. Certainly, this figure is minimal and presents no economic difficulties.

A serious duty then falls on the family physician, who should not only recognize this pertinent problem but should instruct his patients concerning the serious danger of neglecting a complete investigation in every case of hematuria. He will further aid his patients by refusing to prescribe drugs of any type for this condition. Few patients who are made acquainted with the general statistics which have been outlined will fail to heed his warning.





## URINARY INFECTIONS

EDWARD N. COOK

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I HAVE been interested in the visual examination of the urine because of the numerous questions that have been asked me at various times regarding the technic of examination of the urine and also because of the great importance we have learned to attach to such an examination. It is surprising to find how many physicians have almost forgotten the first laboratory test they ever learned. The importance of the bacteriology of the urine has been stressed repeatedly, perhaps more so in the last five or six years than previously. It is definitely of value to the physician and to the patient to know whether or not a coccus or a bacillus is the causative organism in an existing urinary tract infection or whether no organism is present.

When a patient comes to the office the first laboratory procedure should be visual examination of the urine. If the patient is a male, after the glans penis and prepuce have been cleansed with soap and water and alcohol, the patient is asked to void 1 or 2 ounces into a first glass and the remainder into a second glass. In the female only a catheterized specimen is examined, because a voided specimen contains vaginal and cervical secretions which frequently obscure the true picture. If the first glass of urine is cloudy or hazy and the second is clear, it indicates that an anterior urethritis is present with or without involvement of the prostate gland. If the first glass of urine is shreddy and the second clear, chronic urethritis and infection of low grade are present in the prostate gland. If both glasses of urine are cloudy or hazy any of a group of conditions may be present; anteroposterior urethritis, prostatitis, cystitis, pyelonephritis, bacteriuria or phosphaturia. The last can be quickly determined by taking a small sample of

the urine and adding to it a few cubic centimeters of acetic acid. If the cloudiness is caused by the presence of these phosphates it will disappear rapidly. If the first glass of urine is clear, pyuria or bacteriuria is not ruled out because urine often may contain 20 or 30 cells to the high power field and yet appear clear on gross examination.

After the urine in the two glasses has been examined, a sample is taken from the second glass, and is centrifuged for five minutes. The supernatant fluid is drawn off and a drop of the sediment is examined on a clean glass slide to determine the amount of pus, and whether or not erythrocytes, crystalline elements or epithelial débris are present. The importance of the presence of epithelial débris has been demonstrated because in certain cases in which burning and frequency have continued after treatment, examination of the urine has revealed nothing more than a large quantity of old epithelial cells. They have been produced by chemical irritation of irritations. A smear is then made by spreading a drop of urine over the slide and staining with the simple Gram stain. Many modifications of this stain may be employed. Methyl violet may be substituted for gentian violet. Some of the organisms which are commonly found when the urine is examined by this method are: of the bacillary group, *Escherichia coli*, *Aerobacter aerogenes*, *Pseudomonas*, *Proteus*, and so forth; of the cocci, *Streptococcus faecalis* and a green-producing streptococcus are the most common, and organisms of the genus *Micrococcus* and the hemolytic streptococci are less often found. This grouping of the organisms can be identified by the Gram stain. Whether or not the organisms fall into the group of bacilli or cocci is of primary interest for on this will depend the method of treatment.

I would like to consider briefly the various methods of treatment. So far as the urinary antiseptics go, methenamine is, no doubt, the best urinary antiseptic to be administered by mouth. In a test tube the action of this drug depends on an existing pH of 5.5 or less. Ammonium chloride or ammonium nitrate may be employed to increase the acidity of the urine. Methylene blue is of particular value in cases of prostatism. The results with pyridium, hexylresorcinol, and serenium, have not been satisfactory. Potassium permanganate probably is

one of the best solutions to be employed for lavage of the bladder. In cases in which acidification of the urine is necessary, acetic acid, 1:3,000, is helpful. Silver nitrate and mercurochrome have their place in the treatment of infections of the urinary tract. A mild silver protein (argyrol) is of great help in cases of coccal cystitis. Silver nitrate is of value in the treatment of ulcerative cystitis; a 10 per cent solution is first employed and it is increased to 40 per cent. Intravenous injection of neoarsphenamine may be of aid in cases of coccal infections. Usually two or three injections are sufficient. The mode of action never has been definitely proved, but in 65 per cent of cases the organism will be eradicated. Strangely enough, the size of the dose apparently does not make a great deal of difference. At the clinic, 0.45 gm. was administered at first; this amount was reduced to 0.4 gm. and to 0.3 gm. and the results remained the same. Cocci do not grow well in the ordinary media and most of the fancier media. They must be identified by stain and not by culture. Gratifying results have been obtained when mercurochrome was employed, particularly in cases of fulminating pyelonephritis due to a bacillus. Five cubic centimeters of a 1 per cent solution in 500 c.c. of physiologic saline solution has produced seemingly miraculous results and the possibility of distressing colon complications is eliminated if such a mild solution is administered. Methenamine administered with physiologic saline solution has often proved of value.

It is practically impossible to reach a point that is bactericidal by acidification of the urine with drugs. Bacteriostasis may be produced and the patient will be relieved of symptoms by the drug alone. However, in only a few instances has the urine become sterile by the use of an acidulator. The ketogenic diet is still a very useful method in cases of bacillary infection of the urinary tract.

More recently the use of mandelic acid as suggested by Rosenheim has been of great value in the bacillary infections. It is given in a 10 per cent solution and the usual dosage is 2 tablespoonfuls (1 ounce) before meals and at bedtime. The pH of the urine must be adequate (below 5.4) and the fluid intake limited to 1,000 c.c. daily if good results are to be expected.

In summary, the Gram stain will give information as to the causative organism. If it is a bacillus, acidification of the urine by means of ammonium nitrate or the ketogenic diet is perhaps the most effective treatment.

Whenever cocci are found in the urine it is particularly important to eradicate all foci of infection. If infected tonsils or teeth are removed the results are remarkable. I do not believe good results will be obtained in the treatment of coccal infections of the urinary tract as long as any focus of infection remains. The teeth, tonsils, prostate gland in men and cervix uteri in women should be examined.

A third group of cases falls under the category of infections of the urinary tract because the patients respond to treatment for infections. We were taught that sterile pyuria means tuberculosis. During the last year and a half I have been impressed by the number of patients who have come to the Clinic with a diagnosis of tuberculosis which we have not been able to confirm by inoculation of guinea-pigs or by repeated examination of the urine. If foci of infection are removed and the ketogenic diet is administered, the patients do not have further symptoms. I believe the condition is caused by infection because of the response to treatment. The etiology certainly is vague at the present time. Possibly there is a focus of infection somewhere else in the body liberating toxins in the blood stream which may produce a toxic reaction in the urinary tract. The condition may be caused by coccal infection in the cortex of the kidney, with secondary infection in the pelvis of the kidney. Possibly it may be caused by a filtrable virus. Within the last few months a young man came to the Clinic with a diagnosis of renal tuberculosis. Pus was obtained from both kidneys and the bladder was markedly infected. Examination of the urine revealed pus, grade 4. Repeated examination of stains did not reveal *Mycobacterium tuberculosis*. Guinea-pigs which were inoculated with material from the kidneys and bladder did not give evidence of tuberculosis. Treatment in this case consisted of intravenous injection of neoarsphenamine, and tonsillectomy was performed. Six weeks later the urine was crystal clear and the patient did not have any symptoms. Six weeks after he had returned to

his home he had gained 16 pounds (7.3 kg.), and examination gave negative results.

A young girl came to the Clinic because of infection of the bladder. Examination for the gonococcus and *Mycobacterium tuberculosis* gave negative results. Treatment for urethritis was instituted. Two weeks after treatment was discontinued recurrence took place and treatment was again instituted. Four or five days after treatment was discontinued, recurrence again took place. Infected teeth and tonsils were not present. A vaginal discharge had begun just two days before the flare-up in the bladder. Treatment of the eroded cervix was begun and she has been entirely free from symptoms.

The three large groups in which infections occur are cases in which bacillus infection is present, cases in which coccal organisms are present, and cases in which no organism is demonstrable, which are not caused by tuberculosis. This simple method of examining the urine by Gram stain may be most helpful to the physician. It is carried out routinely on every patient who comes to the Section on Urology. We do not wait for the laboratory report but make the examination ourselves when the urine is fresh.

Visiting physician: Do you use the ketogenic diet in cases of acute infections of the kidney? Dr. Cook: No, we do not. The diet is a much more successful means of treatment if it is administered to patients who are up and around than if the patient is confined to bed. Exercise is of definite use in enhancing the value of the diet and producing a greater degree of ketosis.

Visiting physician: Would you include the lower rectum as one of the significant points of foci of infection for cocci? I have seen several cases in which I have wondered if infection of the urinary tract has not been associated with infection of the anal crypts. Dr. Cook: Occasionally such cases will be encountered, but I believe they are rare.

Visiting physician: Do you think that *Bacillus coli* infections are more common in the female than in the male? Dr. Cook: They certainly are more common in female children. In adults they occur equally among men and women.

Visiting physician: Have you used nitrohydrochloric acid?

Dr. Cook: We have found that urine can be acidified with nitrohydrochloric acid and ammonium chloride, but in cases in which acidification cannot be obtained with ammonium chloride the urine will not be acidified with nitrohydrochloric acid.

Visiting physician: Do you limit the amount of fluids in cases of infected urine? Dr. Cook: If the ketogenic diet is employed fluid is limited to six glasses each day. This is important because only a certain amount of ketone bodies will be formed as a result of the diet; if that concentration is lessened by excess of fluid, the desired result is not obtained.

Visiting physician: Is treatment instituted in cases of chronic urinary infections associated with peptic ulcer? Dr. Cook: If the ulcer symptoms are not too pronounced, treatment for the urinary infection is instituted. In one case the symptoms of the ulcer were increased. In six or eight cases a bland ketogenic diet was administered and treatment was completed. I think it is an individual proposition.

Visiting physician: Is ammonium nitrate preferred to ammonium chloride? Dr. Cook: I prefer ammonium nitrate because I do not believe it is as irritating to the gastro-intestinal tract.

Visiting physician: Do you use acriflavine? Dr. Cook: It is used for lavage of the bladder, for instillation and for urethral infections. A solution of 1:3,000 or 1:4,000 of acriflavine is used.

## TREATMENT OF PERSISTENT PYELITIS OF CHILDREN

HENRY F. HELMHOLZ

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PYELITIS as seen in the child is usually a self-limited disease. The tendency to a cure is very evident even in cases in which the course is severe and acute. An illustration of this type of case is the following:

An infant was taken with a fever of 105° F. Physical examination revealed that the throat was intensely red, and that albumin grade 1, pus grade 4, and innumerable *Salmonella* organisms were present in the urine. Fluids were forced. The child was given sodium citrate and sodium bicarbonate, 0.3 gm. of each, four times a day for five days. In a culture made at this time were 400 colonies of *Salmonella* to 0.5 c.c. of urine. A week later there was still pus grade 1 in the urine. A month later the urine was sterile and free from pus.

This case illustrates the importance of careful bacteriologic studies. The type of the infecting organism as well as the number of organisms in a definite amount of urine should be determined. This amount I have taken as 0.5 c.c. When, after one week, only 400 organisms per 0.5 c.c. were found in the urine, it was evident that the patient was overcoming the infection successfully; therefore, further treatment was not given. Otherwise the cure in this case might have been credited to the particular type of treatment employed. Probably a considerable number of infections of the urinary tract run such a course. The infections that persist fall into two definite groups, one in which no evidence of stasis can be elicited on careful urologic examination, and the other in which stasis exists somewhere in the urinary passages. It was thought at one time that the severity of the acute stage had something to do with the persistence of the infection and that the type of organism might be a deciding factor in persistence

isolated from the same individual a varied series of organisms; namely, *Escherichia coli*, *Aerobacter aerogenes*, and *Pseudomonas*. Another common sequence is an infection with *Escherichia coli* which gradually will clear up and leave behind an unmixed infection with *Streptococcus faecalis* which, on continued treatment, disappears. The *Proteus ammoniæ* infections are extremely difficult to treat because of the tendency of the organism to split urea and produce a strongly ammoniacal urine. Experiments performed in vitro reveal that of the common organisms causing urinary infection, the *Proteus ammoniæ* is killed most readily by acidity alone. If the urine can be kept at a pH of 4.8 to 5.0, a urinary antiseptic is not necessary to kill the *Proteus ammoniæ*.

The more the various organisms are studied, and the more that is discovered concerning the bactericidal ranges wherein they are affected, the nearer can physicians come to the most effective therapy.

When stasis in the urinary tract is suspected because of chronic pyuria or bacilluria, difficulty of urination, colic, tumor, or hematuria, the following procedures should be carried out: blood urea, phenolsulphonphthalein output and residual urine should be determined and roentgenograms should be made of the kidneys, ureters and bladder. Then a cystogram should be made. Following this an excretory urogram should be taken. The next step is cystoscopic examination and ureteral catheterization for a culture and differential function, and lastly a retrograde pyelogram. The last part of the program must be carried out by a competent urologist.

In the presence of stasis, the choice of treatment depends on the findings and on the functional capacity of the kidneys. If one kidney is functionless and the other is functioning normally, operation is indicated. If a kidney continues to retain from 15 to 30 per cent of its function and there is a possibility of correcting the obstruction, every effort should be made, first, to eliminate or reduce to a minimum the infection before attempting to restore normal drainage. When this is accomplished hope for partial return of function is justified.

A greater difficulty arises when the lesion is bilateral, and as a result of stasis there has been gradual wearing away of renal function and thus an increase in the blood urea to 50



mg. per cent or more. This condition necessitates a very careful study of the surgical possibilities, if the reduced function is attributable to stasis, or, as is more frequently the case, if it is the result of stasis and infection. If stasis is present, every effort should be made to correct it first because, with impaired function, the urinary antisepsis does not function well, and partial return of function after operation may make its use more successful.

Let me consider, first, a patient who had chronic pyelitis, but whose renal function and urinary tract were normal. The child had had the infection for a number of years, and had had recurring attacks of fever with pyuria. The infecting organism never had been identified and a cure never had been bacteriologically determined. The treatment in a group of cases of this kind can be successfully carried out with methenamine, beta-oxybutyric acid (ketogenic diet) or with mandelic acid acting in an acid medium. Before the ketogenic diet came into use, I was able to show in a large series of cases, in which in some instances the pyelitis had persisted for from three to six years, that the condition could be cleared up rapidly with the use of methenamine and ammonium chloride. The essential feature of the treatment, and one which very frequently is overlooked, is the time that is required for the splitting of the formaldehyde from the methenamine. Methenamine is not bactericidal and is excreted unchanged by the kidney. When it enters the acid urine, formaldehyde immediately begins to split off, and if the  $pH$  of the urine is sufficiently low and sufficient time is allowed to elapse, a bactericidal concentration of formaldehyde will be produced. In studies which I carried out some years ago, I was able to show that bactericidal action was not likely to take place within the limits set by urination unless the  $pH$  of the urine was 5.5 or less.

In order to have a successful reaction with methenamine, a sufficient amount of ammonium chloride must be administered to have the  $pH$  of the urine as low as 5.5 or less. This can usually be done by giving from 0.5 to 1 gm. of ammonium chloride four times a day. When the before mentioned  $pH$  has been reached, as determined by chlorphenol red paper or nitrozone paper (Squibb), it is advisable to start

with the administration of methenamine. The dose is from 0.15 to 0.2 gm. four times a day for infants and from 0.3 to 0.5 gm. for children aged four to five years, and from 0.75 to 1 gm. for children from six to fifteen years of age. After forty-eight hours a culture of the urine is made, and the dosage is continued unless there is evidence of irritation, such as frequency or hematuria. If after another twenty-four hours the culture proves to be sterile, the medication is continued for another two or three days. At the end of this time a culture is again taken to make sure that sterility persists. The medication is then stopped, and after an interval of three or four days another culture is taken. If this is also sterile, the infection has been eliminated.

If after forty-eight hours of treatment, with a urinary pH of 5.5 or less, the urine is still full of bacteria, the dosage of methenamine is increased by 0.25 gm. per dose, and after an interval of twenty-four hours has elapsed, another culture is taken. If bacteria are found again, a similar increase in the dosage is made and this is continued until either a sterile urine is obtained, or evidence of irritation, such as frequency, pain, or hematuria, manifests itself. To attempt treatment without the control by culture is pure guesswork, because the urine may become sterile in twenty-four hours or may not become sterile in two weeks. Sterility can be ascertained only by culture. Treatment with methenamine, if the necessary conditions of time and acidity are observed, can produce a cure in from forty-eight to seventy-two hours.

In the past I have tried this treatment repeatedly for patients with good renal function who had stasis in the urinary passages, but with very infrequent success. Eventually it was concluded that in cases in which this treatment was employed without success, the presence of some anomaly of the urinary tract, which was responsible for obstruction should be suspected. The treatment thus came to be used as a therapeutic test for obstruction. In order to determine beyond doubt the presence of obstruction, cystoscopic examination was necessary but because this was considered a rather formidable procedure in examination of children, it was postponed as much as possible. With better methods of examination of the urinary tract, particularly with the development of excretory

urography, the recognition of obstruction and consequent stasis was greatly simplified. Consequently the practice of prolonged treatment with ammonium chloride and methenamine, as a therapeutic test, was less frequently used.

In contrast to the results of treatment with ammonium chloride and methenamine, treatment with either the ketogenic diet or mandelic acid, even in the presence of urinary obstruction was successful in a larger percentage of cases in which renal function was normal. However, the wisdom of not neglecting to try treatment with ammonium chloride and methenamine was illustrated in a recent experience. A patient was relieved of obstruction of the vesical neck, and the persisting infection with *Streptococcus faecalis* was treated with mandelic acid, but this treatment was not successful. Later nonspecific neoarsphenamine therapy was tried but this was also unsuccessful. Finally, the infection was cleared up by a short period of treatment with methenamine and ammonium chloride. The latter treatment consisted of 0.5 gm. of ammonium chloride and 0.3 gm. of methenamine given four times a day.

The ketogenic diet has been fully explained in numerous papers so that at this time it does not seem necessary to do more than call attention to some salient features of the treatment. Two conditions must be fulfilled in order to obtain a bactericidal urine: (1) the urine must have a  $pH$  of 5.5 or below, and (2) the concentration of oxybutyric acid in the urine must be 0.5 per cent or above. Presence of both of these values can be easily determined. Chlorophenol red paper, and nitrozone paper (Squibb) indicate the proper  $pH$ , whereas the proper concentration of beta-oxybutyric acid is usually indicated by the deep mahogany-red color obtained when 10 per cent ferric chloride and an equal amount of urine are combined. The  $pH$  of the urine has a tendency to rise rapidly after four or five days, and it may be necessary to give ammonium chloride to keep it below 5.5. The ketosis also may become less intense as the body accustoms itself to the high fat diet. The more rapidly the patient can be put into a state of ketosis, the more marked will be the ketosis, so that only two or three days should be allowed to pass before the maximal ketogenic-antiketogenic ratio is instituted. The ketogenic-

antiketogenic ratio of 4:1 usually produces a strongly bactericidal urine. A 1 per cent beta-oxybutyric acid solution is strongly bactericidal at a  $pH$  of 5.5. Concentrations as high as 2.5 per cent have been found. With beta-oxybutyric acid in the latter concentration, and at a  $pH$  of 5.5, probably the urine is the most strongly bactericidal that can be obtained by any means without danger of injuring the urinary tract. Space does not permit me to go into the details of the diet, but experience has proved that only with the help of a trained dietitian is the treatment likely to be successful.

Very much easier to administer and simpler to control is mandelic acid. This organic acid acts in a manner very similar to that of beta-oxybutyric acid. In practically the same  $pH$  range and the same concentrations, mandelic acid acts bactericidally. It is given as ammonium mandelate. If any further decrease in  $pH$  is necessary, ammonium nitrate can be given, or an acid ash diet instituted. Flavored with sarsaparilla it is very well disguised and is readily taken by children, and when diluted with charged water, the product is a very good imitation of root beer.

The bactericidal action of mandelic acid varies inversely as the  $pH$  of the urine and directly as the concentration of the acid. At a  $pH$  of 5, 0.25 per cent of the acid acts bactericidally; at a  $pH$  of 5.3, 0.5 per cent, and at a  $pH$  of 5.5, 1 per cent will act similarly. There is no difficulty in determining the  $pH$  of the urine by means of nitrozone paper or chlorophenol red paper. At present there is no method of determination of mandelic acid except the gravimetric method. It is essential, therefore, to determine the  $pH$  of the urine daily, and to make sure that the urine is in the necessary range below 5.5, because it is not likely that the concentration of the acid will be higher than 1 per cent. If the  $pH$  of the urine on a particular dosage of ammonium mandelate does not drop below 5.5, it is better to add ammonium chloride or ammonium nitrate instead of further increasing the dose of ammonium mandelate. If, on the other hand, the  $pH$  range is right, and after several days' administration the urine does not show signs of reduced bacterial content, it becomes necessary to increase the dose of mandelic acid. Figuring complete excretion in the

urine the approximate concentration in the urine can be calculated from the twenty-hour specimen.

The dose for adults is about 12 gm. per day, 3 gm. given at intervals of six hours. The dosage will depend on the age of the patient. For children up to three years of age, I have begun with a dose of from 0.5 to 1 gm. of the ammonium salt four times a day, and if necessary have increased the dosage to 1.25 gm. four times a day. The child from four to eight years of age should have 1.5 gm. four times a day. Children more than ten years of age start with 2.5 gm. four times a day and can tolerate up to the full adult dose. Ammonium mandelate in these dosages usually will render the urine sufficiently acid to make administration of additional acid-forming salt unnecessary. If the necessary acidity is not reached after two days, ammonium nitrate or ammonium chloride, 0.5 gm. four times a day should be added. Administration of the drug is continued for forty-eight hours testing the pH of the urine each day. After forty-eight hours a culture is taken. If the pH has fallen to between 5 and 5.5 it is likely that the culture will be sterile. If after twenty-four hours, the urine is sterile on culture of 0.5 c.c., the same dose may be continued for another seventy-two hours, the acidity should be checked daily, and cultures of the urine should be made on the fourth or fifth day. If the urine is still sterile, all medication may be omitted, and the urine may be cultured after an interval of seventy-two hours. If the urine is then sterile, the infection has probably been eradicated. If possible, cultures should be made again a week after treatment is discontinued.

When there is no obstruction in the urinary passages this cure is usually permanent. On a number of occasions, when the infection has recurred, it has been eradicated by the same mode of treatment. If the patient's urine remains sterile for a number of days following discontinuance of administration of the drug, the condition should be considered cured. The chronic recurrence of the infection is fairly good evidence that there is some focus which is periodically introducing bacteria, and these, when once back in the urinary passages, can maintain themselves, with or without stasis.

If the infection has been cleared up in a case in which stasis is present, the correction of the stasis should be under-

taken immediately to prevent further injury to the kidneys by back-pressure. When the infection has disappeared, it may be more difficult to persuade the patient or his guardians to undergo the operation, but the advantage of operating on a sterile urinary tract is well worth working for.

The relief of urinary stasis must be left to the urologist, but it should be urged on the patient or his guardians that only by early relief of obstruction can renal function be preserved.

After operation it may again become necessary to sterilize the urine by the administration of ammonium mandelate.

#### SUMMARY

Persistent pyelitis is either the result of faulty treatment or of urinary stasis. During childhood many patients with urinary stasis can be freed from the infection. It is essential to remove the obstruction at the earliest possible moment. Administration of ammonium mandelate, the ketogenic diet, and methenamine, in the order named, are the most useful procedures for combating urinary infections.

## DIAGNOSIS OF ABDOMINAL ENLARGEMENTS IN CHILDREN

SAMUEL AMBERG

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THE size and configuration of the abdomen are determined by the thickness of the abdominal wall and the tonus of its muscles, by its skeletal delimitations and by the characteristics of the contents of the peritoneal cavity. In the newborn infant the transverse and anteroposterior diameters above the umbilicus are greater than in older individuals, and are also greater in relation to the length of the peritoneal cavity and body. During childhood the panniculus adiposus of the abdominal wall of girls is somewhat thicker than that of boys.

During the first years of childhood the abdominal profile usually protrudes further forward than that of the chest. After about the second year, the circumference of the chest exceeds that of the abdomen. Changes in the size of the abdomen resulting from changes in posture are not pertinent to this discussion.

Enlargement of the abdomen may be due to excessive deposition of fat in its walls. Such deposition may be uniform, or the abdomen may be unduly prominent in one place, as for instance in the region below the umbilicus. Deposition of fat may occur as part of constitutional obesity, the etiology of which has hitherto been poorly understood, or it may be associated with endocrine disorders.

The abdomen, for topographic purposes, has been divided into several regions which have been designated the epigastric, umbilical and hypogastric, and the right and left hypochondriac, lumbar, and iliac regions. Enlargement of the abdomen may be evident in only one region, but usually it is more generalized. Enlargement may be due to several factors. For example, a tumor may be present in association with

ascites or with intestinal distention due to obstruction or both. Abdominal enlargement of a high degree can be recognized without difficulty, but enlargement of slight degree may escape notice. The size of the abdomen may be increased by meals, by filling of the intestines, by filling of the bladder, or by accumulation of gas in the intestines. It is therefore not surprising that measurements of the abdomen are omitted in tables of growth and are not mentioned in case reports except when the size is excessive. Parents may fail to note the development of abnormal degrees of abdominal enlargement in children when the enlargement appears gradually.

Enlargement of the abdominal wall as a result of thickening other than that due to obesity may be localized or diffuse. Such enlargement includes inflammatory swellings, with or without abscess formation. Inflammations in the umbilical region of the newborn are now seen only infrequently. Erysipelas occasionally produces swelling of the abdominal wall. Erysipelas has been seen in two infants, extending from the vulva to the abdominal wall; in the course of the illness purulent peritonitis and dynamic ileus developed, after which most of the abdominal enlargement was attributable to their presence. The diagnosis in such cases is usually self-evident. Peritonitis in the newborn infant can originate in infections in remnants of the omphalomesenteric arteries or of the umbilical vein. The point of origin, under such conditions, may not be recognizable during life. Localized enlargements may be caused by congenital umbilical hernias; for instance, a hernia into the umbilical cord may be very large, and in addition to intestinal loops, may contain other organs such as the liver. Tumors of the umbilicus in the newborn are usually small. An umbilical hernia may progress to partial or complete eventration, which in turn may be accompanied by distention of the intestines.

Angioneurotic edema can occur in the abdominal wall and thus produce localized single or multiple regions of enlargement. Recognition of such swelling as urticarial may be aided by the presence of urticaria-like swellings in other regions of the body, by their transient nature, and by their itching.

Definitely localized enlargements may be caused by tumors of the abdominal wall. A good illustration of such enlargements, resulting from a neurofibroma, is given in



Schultz' chapter on tumors in children in Abt's System of Pediatrics. Lipomas can also produce enlargement of the abdominal wall.

Diffuse enlargement of the abdominal wall, if not attributable to obesity, is usually due to edema, which may be very marked. It occurs most frequently in patients suffering from circulatory failure, from nephrosis, or from nephritis. Edema of the abdominal wall in cases of hepatic disease is usually not so great. It may become more prominent as the disease advances. Often in such cases the enlargement of the abdomen is due not only to edema of the wall but also, to some extent, to peritoneal effusion. In cases of nephrosis, acute peritonitis may supervene, thus adding distention of the intestines to the already present enlargement. Clinically it is not always easy to distinguish edema of the abdominal wall from peritoneal effusion, or to estimate how much of an enlargement is due to one or the other factor. In testing for undulation it is well to have an assistant exercise linear pressure on the middle of the abdomen. At times edema of the abdomen of the newborn infant occurs as part of hydrops universalis. This is also usually accompanied by peritoneal effusion. Such infants when not stillborn, die within the first few days of life. There is another form of edema accompanied by peritoneal effusion which occurs rarely during infancy. The etiology is unknown.

Lack of tone of the muscles of the abdomen may result in its enlargement. The abdominal distention of rickets, celiac disease and occasionally of diseases of the central nervous system such as infantile paralysis, has been ascribed in part to weakness of the abdominal muscles.

Enlargement may be caused by disease of one or the other of the organs located within the peritoneal cavity. Such enlargement may be unilateral, or limited to a particular region or regions. Thus, diseases of the liver may be associated with prominence of the right hypochondrium and the epigastrium. Hypertrophy of the liver in cases of cirrhosis can produce fullness in these regions, although a considerable degree of enlargement of the liver may be present without producing definite fullness until portal hypertension results in ascites. In one of our cases at the clinic, that of a boy aged twelve years, a visible tumor-like mass was present in the epigastrium. It

proved to be the left lobe of a cirrhotic liver. Syphilis of the liver may also produce visible enlargement.

In infants and younger children enlargement of the abdomen may be secondary to enlargement of the liver by fatty infiltration, or by excessively large deposits of glycogen ("glycogen storage disease," Van Gierke). In such cases the values for fasting blood sugar may be below normal and may rise little or not at all on administration of epinephrine.

In infants, Niemann-Pick's disease, a type of reticulo-endotheliosis, may be associated with enlargement of the liver of sufficient degree to cause visible protrusion of the abdomen.

Tumors of the liver may produce bulging of the abdomen. Primary carcinoma and sarcoma of the liver occur even in early infancy. Hemangiomas and hemangio-endotheliomas, although of uncommon occurrence, have been observed most frequently in early infancy. Leukemic infiltrations and Hodgkin's disease of the liver may cause the abdomen to protrude over the site of that organ. This may happen also in some forms of anemia, such as Cooley's. Metastatic tumors such as neurocytomas from the suprarenal gland may also cause visible protrusion.

Multiple abscesses of the liver very rarely cause visible enlargement of the abdomen in children. Abscess of the liver due to *Endamæba histolytica* is not common in childhood. Such an abscess may occasionally become so huge as to cause visible enlargement of the abdomen and fluctuation. The diagnosis usually depends on a history of dysentery and on the demonstration of amebas in the stools.

Cysts of the liver sometimes cause very marked abdominal distention. An instance of this was observed in the case of a girl, aged three years, whose abdomen had gradually enlarged. On palpation a circumscribed fluctuating tumor was found, which seemed sharply separated from the liver. The clinical diagnosis of ovarian or mesenteric cyst was not substantiated at operation, at which time a large cyst of the liver was found. The liver was very large and contained at least one other large cyst. The larger cyst was drained, and continues to discharge after eight years. The abdominal enlargement has decreased and the girl now regularly attends school. This case illustrates the fact that when a cyst is so large as to fill the ab-

domen, it is hardly possible to determine the organ from which it takes its origin. In the earlier stages of development of a tumor, the location as determined by palpation may help to determine the organ from which it originates as well as its probable character. In contradistinction to solitary cysts, which may be single or multiple, generalized cystic disease of the liver may be present and may cause visible enlargement. The solitary cysts may be lined with ciliated epithelium. Cysts of the liver may be caused by echinococci. The finding of a specific precipitin reaction of the patient's serum or a positive Casoni cutaneous reaction is of great value in the diagnosis.

During childhood, diseases of the large bile ducts or of the gallbladder rarely lead to visible change in the contour of the abdomen. Cysts of the common duct, of unusually large size, may cause visible swelling. If pain and intermittent attacks of jaundice are associated with such visible swelling, they may aid in the preoperative diagnosis.

Very rarely a cyst of the pancreas may become sufficiently large to cause abdominal enlargement.

The spleen may enlarge so greatly as to be visible. This may occur in patients with malaria, and in patients with leukemia, particularly the myeloid form. In both instances, examination of the blood should give information on which a definite diagnosis can be based. The same remarks apply to kala-azar, which is very rare in the United States. Visible enlargement of the spleen may be present in the course of familial hemolytic icterus, particularly during a crisis. Very marked enlargement of the spleen may be associated with thrombophlebitis of the splenic vein. The vascular occlusion may be suspected if hematemesis occurs early in the disease. If such a splenic tumor becomes palpably smaller after intramuscular injection of epinephrine it is likely to be due to vascular obstruction. Malignant disease, primary in the spleen, as for example sarcoma, is extremely rare.

An enlargement of the spleen may become visible in Gaucher's disease which can occur in childhood. Cysts also occur in the spleen. The tests already mentioned may be used to determine whether such cysts are due to echinococci. Echinococcus cysts of the spleen are much more rare than

echinococcus cysts of the liver. In the case of a boy, aged eight years, a diagnosis of cysts of the spleen was based on the findings of bulging of the left hypochondrium and flank and splenomegaly. The diagnosis was confirmed at operation. The cyst contained blood. The histopathologic diagnosis was not positive; it was thought to be hemangioma. The cause and often the exact nature of such splenic cysts is obscure, and the diagnosis is often made only at the time of exploratory operation. In the case just cited, the mother noted abdominal swelling ten months before her son's admission, and jaundice, of a week's duration, six months before admission.

Enlargement of the organs of the genito-urinary tract as a result of disease may cause abdominal enlargement. It is a well known fact that a distended urinary bladder may cause prominence of the lower part of the abdomen, and that such prominence is not always in the midline. It may be found at any age. Catheterization, or catheterization and manual expression, will result in prompt disappearance of the swelling. Ureters which are greatly dilated may lead to some fullness of the lower part of the abdomen. It is also common for a hydronephrotic kidney to cause bulging of the abdomen. This bulging is usually unilateral and in the flank. Disappearance of the swelling following copious urination should suggest the diagnosis, which, like that of a megalo-ureter, can be definitely established by urologic examination.

Cysts of the kidneys may be of sufficient size to cause abdominal enlargement. They may be unilateral or bilateral. If they are of the solitary type they may not interfere with the function of the kidneys. The location and consistence may suggest the true nature of the swellings. Since they are not radiosensitive, therapeutic application of roentgen rays is of aid in differentiating them from malignant tumors of the kidneys.

Malignant tumors of the kidneys of children are not extremely rare. They are usually of a mixed type and are often designated as Wilm's tumors. Children with Wilm's tumors frequently are not brought to a physician before abdominal fullness has become noticeable. The tumors are usually very firm, although they may contain cystic areas of degeneration. Hematuria is of infrequent occurrence in patients with Wilm's

tumor, but if present, is of diagnostic importance. A roentgenogram of the abdomen or urologic examination may reveal distortion of the renal pelvis, which is of diagnostic help in localizing renal tumors of a cystic kind, or other kinds.

Cysts of the urachus have been found in children with abdominal distention. The diagnosis in some cases is uncertain and can hardly be made without exploratory operation. Tumors of the bladder that cause abdominal enlargement in children are very rare. Occasionally a malignant tumor of the prostate gland, such as a sarcoma, may cause abdominal enlargement, which is made up in part by metastatic nodules, by ascites, by distention of the intestines, and by edema of the wall. These tumors, too, are of very infrequent occurrence in children. The first symptom may be dysuria. Catheterization may be difficult because of obstruction. A mass may be palpable by rectal examination.

Tumors of the ovaries, especially cysts, are more common in children. Because of their presence, abdominal enlargement may be very great. The finding of a circumscribed tumor which arises from the midline of the pelvis, which is circumscribed and which dents readily but does not exhibit movable dulness, should suggest the presence of an ovarian cyst. A large flaccid cyst may simulate ascites with undulation or ascites which is so marked as to exhibit no movable dulness. Other malignant tumors may arise in the ovaries. We at the Clinic have seen a teratoma attached to the wall of the bladder of a girl aged eight years, whose abdomen below the umbilicus was considerably enlarged. If roentgenograms reveal the presence of bony material in such tumors, their nature may be more strongly suspected.

Affections of the intestinal tract often account for enlargement of the abdomen. With the exception of umbilical hernias which, in infants, do not often attain great size, direct hernias through the abdominal wall in children are rare. Occasionally a large, postoperative direct hernia may develop. Enlargement of the abdomen that takes place following incarceration of an intra-abdominal hernia is due primarily to the intestinal obstruction.

In young children, pyloric stenosis or obstruction of the duodenum may cause a protuberance in the epigastrium. The

visibly distended stomach may make the upper part of the abdomen of an emaciated infant very prominent as compared to the sunken-in lower portion. The diagnosis of pyloric stenosis is aided by the presence of visible peristalsis of the stomach with waves that travel from left to right, by projectile vomiting and, less frequently, by a palpable mass in the region of the pylorus. After operation visible distention of the stomach may take place. This occurred in the case of one infant operated on for pyloric stenosis.

In some instances abdominal enlargement results from distention of the intestine above the point of an obstruction, partial or complete. The obstruction may be caused by congenital atresia. If atresia involves the anus, intestinal stasis and distention are usually absent because the fistulous channel that develops between the rectum and urinary tract allows escape of intestinal contents. Partial obstruction of the intestine may be due to a variety of lesions, such as incarcerated hernias, fibrous bands that constrict one or more loops, volvulus, tumors both extrinsic and intrinsic, and segmental inflammation. In addition to causing distention of the bowel, obstruction may cause visible peristalsis of the dilated portion, and borborygmi may be very noticeable. If the obstruction becomes complete, the abdominal distention may be very great. Cessation of bowel movements, absence of fecal matter from the lower part of the intestine, vomiting of fecal material, rapidly developing emaciation and desiccation, are the most striking features of such mechanical ileus.

In older infants acute intussusception is perhaps the most frequent cause of partial or complete intestinal obstruction. Intermittent attacks of apparently severe pain, which begin suddenly and which are associated with crying, particularly at the age at which the infant begins to walk, are often the first symptoms. Soon after the appearance of these symptoms blood or bloody material is passed from the rectum. The child may vomit. Between attacks of colicky pain when the abdomen may be soft, a sausage-shaped mass may be palpated. This is usually felt first in the right ileocecal region. Fluoroscopic examination together with inflow of contrast material can be of great value. After a shorter or longer period of time the intestines and abdomen become distended. Intussuscep-

tion may occur also in later childhood. Chronic intussusception occurs much less frequently, and is usually initiated by some lesion of the intestinal wall such as a polyp. In one case observed at the Clinic a lymphoma was the cause of chronic intussusception which was associated with a considerable degree of abdominal distention. The clinical picture may be difficult to analyze.

Intra-abdominal cysts may originate from a Meckel's diverticulum, or from some other part of the intestines, from the mesentery, or from the omentum. These, even in very young patients, can cause abdominal enlargement, either by their size or by causing intussusception or obstruction. We have observed a cyst of the omentum in a girl aged four years. An enlarged abdomen was noted about ten months before admission. On examination a large, rather flaccid cystic mass was found. At operation two rather large cysts were found: the larger contained 2,800 c.c. of bloody fluid. The smaller cyst was ruptured during operation. Cysts of the mesentery are likely to be multiple.

Tumors of the intestines may be responsible for abdominal enlargement. The most common types are lymphomas or lymphosarcomas. In the case of a boy, aged thirteen years, the cause of abdominal distention was found to be widespread lymphosarcomatosis of the intestines and mesentery. In this case the distention was due to the presence of fluid in the peritoneal cavity as well as to the presence of the tumors.

Abscesses within or adjacent to the peritoneal cavity may be of sufficient size to produce abdominal enlargement. This may occur, for example, in the case of a psoas abscess of tuberculous origin. The finding of tenderness over the spinal column and the demonstration by roentgenography of a lesion of the vertebrae are of major importance in determining the nature of the process. If in such a case the intracutaneous tuberculin reaction is repeatedly negative, a diagnosis of tuberculosis becomes uncertain. Appendicitis, with perforation of the appendix, is perhaps the most frequent cause of enlargement of the abdomen due to purulent exudate in the peritoneal cavity. Following subsidence of the immediate generalized inflammation, localized protrusion of the abdomen may become visible. This is present most frequently on the right side of

the abdomen, but it may extend beyond the midline and may even be more prominent on the left side. A history of pain and tenderness in the region of the appendix is of the greatest value in diagnosis. The character of the temperature curve and the blood picture will probably indicate the purulent nature of the condition. Large abscesses may come from other sources, such as areas of osteomyelitis.

Enlargement of the abdomen due to distention of the intestines without obstruction occurs very frequently. Pain, if present, disappears as flatus escapes from the bowel. Distention of this sort as a rule does not persist. Palpable masses, tenderness, and signs indicative of effusion are lacking. It is of frequent occurrence during the course of infectious diseases such as pneumonia and may contribute to embarrassment of respiration. It is of not infrequent occurrence after operations. This kind of distention combined with weakness of the abdominal muscles has been thought to account for abdominal enlargement in rickets and in celiac disease. Persistent distention of segments of the small intestines may occur without any demonstrable cause.

The most marked degrees of abdominal enlargement are found in cases of Hirschsprung's disease (megacolon). A thin abdominal wall, resulting from the emaciation which is usually present, allows the pattern of the intestinal loops and their peristaltic constrictions to be easily visible. The enlarged abdomen may be pear shaped, with the wider portion uppermost. A history of absence of spontaneous bowel movements from the time of birth or early infancy is of greatest diagnostic significance. In some cases canalization of the retained fecal material may permit the occurrence of diarrhea. The huge masses of retained fecal material are usually palpated with ease, and after repeated and properly administered enemas they disappear. Roentgenologic examination of the colon is of great value in diagnosis. However, a false impression of dilatation of the colon may be obtained from examination of the roentgenogram alone. It is therefore very important, particularly when the diagnosis is somewhat doubtful, to have a fluoroscopic examination. It is also of importance to decide whether the dilatation involves the entire colon or only a segment of the colon. On this finding may



rest the decision as to the advisability of sympathectomy or resection of the colon.

An excessive amount of fluid in the peritoneal cavity, either alone or together with other factors such as distention of the intestines and tumors, is a very frequent cause of abdominal enlargement. Excessive amounts of fluid may accumulate as a result of inflammatory processes of the serosa, diseases of the kidneys, or interference with the circulation of blood and lymph. The character of the fluid differs according to the source and cause of its derivation. If the fluid is a transudate, such as that formed in cases of circulatory obstruction, the protein content will usually be found to be less than 3 or 4 gm. per 100 c.c. If the fluid is composed of inflammatory exudate, the protein content is greater. The lowest value for protein content, 0.5 gm. per 100 c.c. or less, is found in the opalescent ascitic fluid from patients with lipoid nephrosis. In cases of nephritis and in cases in which there are circulatory disturbances the fluid is usually clear. An exception to this is the fluid from patients with chylous ascites, but this is very uncommon. The ascitic fluid in this condition is milky, and if ether is added to it, it becomes clear. In the presence of tumors the ascitic fluid may be brown or bloody.

Free fluid in the abdomen, if not too great in amount, is indicated by dulness to percussion. This dulness moves as the patient changes position. If the abdomen becomes tense because of the accumulation of fluid, percussion will yield a note which is dull regardless of the position assumed by the patient. In such cases the presence of fluid can be more reliably determined by the elicitation of undulation, or fluid waves, by the proper maneuver. It has been mentioned that large cysts with flaccid walls may be confused with collections of fluid in the peritoneal cavity.

Large amounts of fluid may be associated with protrusion of the navel.

Circulatory disturbances which lead to the accumulation of fluid may be divided into two main groups: those due to portal hypertension, and those in which the circulatory obstacle is intrathoracic. The latter may be either a failing heart or narrowing of the inferior vena cava in patients with adhesive pericarditis.

Portal hypertension resulting from thrombosis of the portal vein occurs rather infrequently, particularly in children. In such cases the ascites develops rapidly. However, this may occur in other conditions. I saw one case in which thorough exploration did not reveal an adequate explanation for the rapidly developing ascites.

Portal hypertension as a rule is due to diseases of the liver which will be designated here collectively as "juvenile cirrhosis" without any attempt to subclassify. As fluid accumulates from any cause, the abdomen distends and the navel may protrude. In cases of portal hypertension, visible collateral circulation in the umbilical region, the caput medusæ, is commonly observed. This need not occur in every case, since the path of the collateral circulation may be deep in the abdominal cavity. Collateral circulation visible on the sides of the abdomen is more likely to be caused by an obstruction in the abdominal, inferior vena cava. Edema of the lower extremities and of the abdomen may occur late in the disease and may be due to various factors which do not concern us here. A history of jaundice, early enlargement of the spleen (common in juvenile cirrhosis), and various tests of liver function, aid in the diagnosis. The liver is usually enlarged.

In very rare cases congenital obstruction of the hepatic veins at their entrance into the vena cava may exist and may lead to abdominal enlargement. Obstruction of the vena cava in cases of adhesive pericarditis or "inflow stasis" is not always easy to differentiate from portal hypertension. The disease is more common in later childhood and early adolescence. Signs of valvular heart disease may be absent. In patients with constrictive pericarditis the respirations are usually easily embarrassed; there may be some cyanosis, and edema of the lower extremities may appear early in the course of the disease. Venous pulsation in the neck occurs only. Effusion into the pleural cavities is not an uncommon finding. In the few cases which I have seen, no collateral circulation was visible. The sluggish circulation causes the liver to enlarge soon after the onset of the disease. In one of our cases at the Clinic the surface of the liver became uneven and signs of impaired liver function were found. In this case a considerable degree of obstruction was found at operation. The constricting tissue was

partly calcified. In another case calcification of the pericardium was visible in the roentgenogram. The only effective treatment is surgical.

Ascites that develops in patients with nephrosis is usually associated with edema of the legs and abdomen. The urine usually contains considerable amounts of protein and large numbers of casts, and may contain lipoids which are doubly refractive. Increased values for blood lipid and cholesterol are of diagnostic significance. Other forms of ascites due to renal disease can be differentiated from nephrosis by the different findings in the urine, by the presence of elevated blood pressure, and by the demonstration of impaired renal function.

Obstruction of lymph channels may cause chylous ascites. In the case of a boy aged eight months, enlargement of the abdomen was found to be due to such an ascites. At necropsy the thoracic duct could not be demonstrated.

The subject of tuberculous peritonitis deserves special attention. It occurs in the two main forms, the dry and the ascitic. However, there may be a combination of these. The ascites usually develops insidiously and may be accompanied by progressive emaciation. It has been stated that rapidly developing ascites in children is usually due to tuberculous peritonitis. This may be true in regions in which tuberculosis is unusually prevalent. Pain and tenderness frequently are absent. The onset may be stormy, and may simulate that of an infectious disease like typhoid fever, or it may be gradual as in other forms of acute peritonitis. The dry form is characterized by the formation of fibrous tissue. Abdominal enlargement may be the first and only symptom. The intestinal coils, thickened by fibrotic tissue, may form irregular protruding masses. The omentum may become fibrotic and cause protrusion of the upper portion of the abdomen. The enlargement of the abdomen may be increased by ascites which is sometimes transitory in nature. The diagnosis of tuberculous peritonitis is made more probable by a history of contact with tuberculosis, by the demonstration of tuberculous lesions elsewhere in the body, and by a positive intracutaneous tuberculin reaction. If tubercle bacilli can be demonstrated in the fluid or lesions the diagnosis becomes certain. Guinea-pig inoculation is usually required for such proof.

Purulent peritonitis may be due to a variety of organisms, of which streptococci, pneumococci and colon bacilli are the most common. The mode of invasion is not always apparent. It may occur as a result of perforation of the intestinal tract by trauma or ulceration. The organisms may reach the peritoneum through the blood stream, through lymph channels, from a ruptured abscess, or possibly by transmigration. The diagnosis of acute purulent peritonitis is relatively simple in cases with the characteristic increase of muscle tension, the pain, the rebound tenderness, the vomiting, fever and polymorphonuclear leukocytosis. Usually there is constipation, but there may be diarrhea. It is well to remember that the picture may not be complete. Enlargement of the abdomen is usually due more to distention of the intestines than to the amount of purulent fluid. If the peritonitis is due to pneumococci, the amount of pus may be sufficiently large to produce abdominal enlargement. Diagnostic aspiration of the intraperitoneal material has been recommended.

Abdominal enlargement due to hemorrhage into the peritoneal cavity may occur after trauma. The most frequent cause is rupture of the spleen. The history of an injury, the location of the injury, and evidence of rapid loss of blood are the most important diagnostic features. Definite diagnosis usually cannot be made before exploratory operation is performed.

## DISEASES OF THE THYROID GLAND IN CHILDREN

ROGER L. J. KENNEDY

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IN order to understand better the morbid processes that occur in the thyroid gland and the clinical disturbances which result from these processes, it is well to have in mind certain facts concerning the anatomy, embryology, histology and physiology of that organ.

The gland is bilobed, the lobes being connected by a bridge of tissue, the isthmus, which crosses the midline of the neck, anterior to the trachea. Ordinarily, the lobes cannot be outlined by palpation, although the isthmus is frequently palpable and even visible.

The size of the organ varies with age, from birth to puberty. In the newly born it weighs from 1.5 to 2.5 gm. The weight increases to about 10 gm. by the tenth year and to about 15 gm. at puberty.

Four main arteries, two superior and two inferior thyroid arteries, together with the thyroid ima artery and other lesser arteries, carry the blood supply to the thyroid. The veins which arise in a rich plexus covering the gland, are the superior, lateral and inferior groups.

The gland receives its nerve supply from both the sympathetic system and the vagus nerves, chiefly from the former. The close relationship between the gland and the recurrent laryngeal nerve is of considerable clinical and surgical importance.

Accessory thyroid glands may be formed along the course of the thyroglossal duct, from the base of the tongue to the root of the neck. If the thyroid fails to progress in development beyond the tongue, there results an aberrant lingual thyroid. The close apposition of the thyroglossal duct to the hyoid bone accounts for the occurrence of accessory thyroids in the

region of the bone. This too accounts for the position of thyroglossal duct cysts (Fig. 38) and sinuses which are always in the median line near the hyoid bone. Other accessory thyroids may be found in close approximation to the pyramidal and lateral lobes and at the lower pole of the gland. From these may arise intrathoracic and retrosternal goiters.



Fig. 38.—Thyroglossal duct cyst of a boy aged twelve years. The cyst had been incised, following which it had healed and discharged intermittently. The characteristic position in the midline of the neck is well illustrated and serves to distinguish thyroglossal duct cysts and sinuses from brachial cleft and other kinds of cysts.

The occurrence of a pyramidal lobe or of a persistent thyroglossal duct is based on the following embryologic facts. The thyroid arises from the floor of the pharynx. It develops as a stalk with a globose end. Under ordinary conditions the stalk becomes obliterated and the globose end develops into the bilobed gland. If the connection between the stalk and the pharyngeal floor is lost near the pharynx, a pyramidal lobe or persistent thyroglossal duct may result.

The parenchyma of the gland consists of colloid-filled fol-

licles. The follicles are lined with epithelium made up of cuboidal cells.

The function of the thyroid gland, according to Plummer (1922), is the elaboration and delivery to the blood of a secretion containing its active principle, thyroxin, and the storage of colloid in its vesicles. Iodine is probably stored in the colloid.

When inorganic iodine is injected or given by mouth, it is taken up rapidly by the thyroid gland. Iodine in the inorganic form, however, is not present in the normal gland; it is found there only as a component part of organic compounds (Kendall). From 0 to 15 per cent of this organic iodine of the gland is to be found in thyroxin; the balance of the iodine is present in other compounds.

Iodine is present in the gland even before birth and increases in amount from birth to maturity. The amount is determined to some extent by the content in the diet and water supply. Sea foods are known to have a relatively high content of iodine. In order to maintain the required amount in the gland, a child must receive daily from 0.050 mg. to 0.150 mg. of iodine.

According to Plummer (1926) thyroxin functions throughout the cells of the body and does not primarily influence any one organ or system of organs. It functions not by producing energy itself, but by raising the capacity of any given cell to respond to excitation or stimulation.

If the thyroid gland is removed from young animals a striking series of changes takes place. There is retardation of growth and depression of all of the physiologic functions of the body. Growth of bone slows up, the hair becomes dry and coarse and the muscles become weak and flabby. Movements become sluggish. The temperature is lowered and pulse slowed. Sexual function fails. There develop an increased tolerance for carbohydrates and an increased storage of glycogen in the liver. The basal metabolic rate is lowered as much as 40 per cent or more.

Thyroidectomy in children is followed by a picture similar in all respects to that observed in young animals. In addition to retarded physical growth and depressed physiologic functions, various kinds and degrees of mental disturbance may

develop. Examination of an individual so affected may reveal a sluggish, apathetic, sleepy person. The hair may be coarse, the skin dry, the features heavy, and the expression dull. The body temperature is low, the perspiration decreases, the patient may complain of sensitiveness to cold, and anorexia and constipation are common. Pads of tissue, simulating fat, appear especially above the clavicles. These are referred to as myxedematous pads, the nature of which is unknown.

Feeding of large amounts of thyroxin to young animals does not result in a condition exactly the reverse of that brought about by insufficient thyroid material. There is a diminished rate of growth and hypertrophy of certain organs such as the testes and ovaries, the suprarenal glands, the heart, the liver, the pancreas and the spleen. The thyroid gland decreases in weight and activity, although the metabolic rate increases. If feeding of thyroid is discontinued, the rate of growth is accelerated and hypertrophy of the organ subsides.

Administration of large amounts of thyroid material to human beings is seldom continued for any length of time. It results in serious phenomena such as tachycardia and arrhythmia, vertigo and weakness, excessive perspiration, diarrhea and generalized pains.

In young individuals, from whom the thyroid glands have been completely removed, restitution to normal can be brought about by administration of thyroid material. If young individuals have been deprived of thyroid material for some time, the restitution will be only partial.

Complete absence or lack of function of the thyroid gland results in lowering of the basal metabolic rate to a level of from 40 to 45 per cent below the average of normal individuals. In patients whose thyroid glands are overactive the basal metabolic rate may be elevated to as much as 100 per cent above normal. In recent years considerable investigative work has been done which is purported to demonstrate certain relationships between the glands of internal secretion. Perhaps the most important of these concerns the claims which have been made for the existence of a hormone, the so-called "thyrotropic hormone," present in the pituitary gland, which controls the activity of the thyroid gland. In spite of the evidence that has been offered to support the claim of the existence of such



a hormone in lower animals, there is very little evidence that it is present in human beings, or if present, that it is of any clinical importance.

### DISEASES OF THE THYROID GLAND

As a working classification of diseases of the thyroid glands of children, the following is offered:

- Congenital goiter
- Diffuse colloid goiter
- Adenomatous goiter (without hyperthyroidism)
- Exophthalmic goiter
- Hypothyroidism
- Cretinism { Athyreotic
- Endemic
- Myxedema
- Inflammation (thyroiditis)
- Malignant diseases of the thyroid.

#### CONGENITAL GOITER (CONGENITAL HYPERTROPHY, NEONATAL STRUMA)

Congenital goiter, which consists of enlargement, in part or in whole, of the thyroid gland of the newly-born child, is to be distinguished from the enlargement attributable to congestion and from that found in patients with endemic cretinism. The upper limit of weight of the thyroid gland in newly-born infants varies in different countries from 2.5 gm. up to 6 gm. Weights exceeding these figures are probably abnormal and the glands represent congenital goiters.

Deficiency of iodine in the mother may be responsible for goitrous infants. Since the incidence is higher in regions where goiter is endemic than elsewhere, it may be assumed that the causes, whatever they may be, are the same as those which produce other endemic goitrous diseases.

The gland, in part or in whole, is large, firm and regular or irregular. Dyspnea of varying degree may be present. Death may result from obstruction of the respiratory tract.

In general the more marked the enlargement, the greater is the danger to the life of the infant; the mortality may be as high as 60 per cent. Usually there is spontaneous regression in the size of the gland.

The administration of iodine in a dose of 10 mg. three times

a day to a pregnant woman, from the third or fourth month antepartum, has been advised to eliminate the possibility of congenital goiter.

Intubation, tracheotomy and resection of the thyroid isthmus have been employed in treatment. If the enlargement persists beyond the first few weeks of life, treatment with iodine and thyroid material may be administered.

#### GOITER (STRUMA, BRONCHOCELE, DIFFUSE COLLOID GOITER)

The term, "diffuse colloid goiter," indicates a diffuse symmetrical enlargement of the thyroid gland (Fig. 39), the acini



Fig. 39.—Diffuse colloid goiter of a boy aged seven years. *a*, Before, and *b*, two months after start of desiccated thyroid therapy. In addition to diffuse enlargement of the thyroid gland, there was a lowered basal metabolic rate ( $-20$  and  $-22$ ) and clinical evidence of hypothyroidism. The blood cholesterol at the time of admission was 211 mg per cent. Roentgenograms of the wrist showed delayed ossification of the carpal bones. Reduction in the size of the gland and marked general improvement resulted promptly from treatment.

of which contain an excess of colloid; the enlargement is unassociated with symptoms of hyperthyroidism. It is variously referred to as "adolescent," "adolescent colloid," "vascular

colloid," "vascular adolescent colloid" and "simple" or "endemic goiter without adenomas or hyperthyroidism." Although endemic in some areas, it may be found in any part of the world.

Diffuse colloid goiter is the type of enlargement of the thyroid gland that has served as the subject of many surveys among children, particularly of those at or near the age of puberty. The use of different standards for diagnosis has resulted in some difference of opinion regarding the incidence of the condition. Suffice it to say that definite enlargement of the lobes of the thyroid gland has been of common occurrence among children, especially of those at or near the age of puberty.

The cause of this enlargement has not been definitely established, although the view that it is attributable to some deficiency, probably of iodine, is generally entertained.

The symptoms and signs which it may cause are chiefly local. The gland is found to be smooth and bilaterally and symmetrically enlarged; the enlargement may be slight or extreme. The gland is soft and compressible. The superior thyroid arteries may be so large as to be palpable, and a bruit and thrill may be present. The patient may complain of a feeling of fullness in the neck. The basal metabolic rate may be slightly depressed.

Sometimes the gland recedes spontaneously. By treatment it can usually be made to recede within a year. If such glands of children have been reduced the children should be given prophylactic doses of iodine for several years afterward, in order to prevent return of the enlargement. Exophthalmic goiter, contrary to certain expressed beliefs, is not more likely to occur in patients who previously had an existing diffuse colloid goiter.

The prophylaxis of goiter is concerned chiefly with the diffuse colloid type. The most important prophylactic measures which have been employed are the addition of iodine to water supplies, the use of iodized table salt, the use of tablets that contain iodine (iodostarin tablets contain 1 to 4 mg. of iodine), the use of compound solution of iodine (Lugol's solution) (from 3 to 5 drops once a week), the use of hydriodic acid (1 teaspoonful once a week), and the use of desiccated

thyroid. Iodized table salt, which is now so commonly used, is probably the simplest and most economical of the prophylactic preparations.

In the early stages of the development of the condition iodine in prophylactic doses may be curative. Desiccated thyroid gland administered orally in a dose of 1 to 2 grains (0.065 to 0.12 gm.) daily is the treatment of choice in well developed cases. In order to check the potency of the thyroid preparation and to maintain the metabolic rate at or near normal, it is desirable that frequent determinations of the basal metabolic rate be made. Only rarely need children be operated on.

#### ADENOMATOUS GOITER WITHOUT HYPERTHYROIDISM

Adenomatous goiter is a nodular enlargement of the thyroid gland caused by the presence of single or multiple aden-



Fig. 40.—Colloid and fetal adenoma in a diffuse colloid goiter of a girl aged twelve years. Nodules of this sort are rare among children and in our experience have more frequently been proved to be malignant than benign. The appearance may be similar in all respects to that of malignant nodules

omas within its substance (Fig. 40). Although in adults it is frequently accompanied by symptoms of hyperthyroidism, in

children it causes no constitutional symptoms. In other words, the syndrome of adenomatous goiter with hyperthyroidism has not, in our experience at the Clinic, been observed in children.

Although adenomatous goiters of clinically recognizable size occur with greater frequency in regions where goiter is endemic than elsewhere they are rare among children in the United States. They may occur in diffuse colloid goiters and remain unrecognized until the excess colloid disappears spontaneously or following treatment. The fact that they are more common in regions where goiter is endemic than elsewhere indicates that their etiology is the same as that of diffuse colloid goiter.

The adenomas give rise to few signs or symptoms other than visible and palpable nodular swelling of one or both lobes of the thyroid gland. Symptoms that result from pressure on the trachea or on the recurrent laryngeal nerve may be produced, and may be not only troublesome, but even serious.

Pathologically, the adenomas may be of the encapsulated ("fetal" or "adult") type, or as some observers hold, they may consist of noncapsulated nodular portions of thyroid tissue.

Removal of adenomas of the thyroid gland of children is justified for two reasons. Later in life the adenomas may require excision because of hyperthyroidism. Probably of even greater importance is the fact that carcinoma may be present in an adenoma without giving any indication of its presence. Timely removal of such a nodule offers a very good probability of complete cure.

#### EXOPHTHALMIC GOITER (GRAVES' DISEASE, BASEDOW'S DISEASE, PARRY'S DISEASE, HYPERTHYROIDISM, AND THYREOTOXICOSIS)

Exophthalmic goiter, according to Plummer's conception, is a clinicophysiologic complex similar to "that following the administration of thyroxin, or that associated with hyperfunctioning adenomatous thyroid, plus certain characteristic findings that can be grouped as ocular symptoms, the characteristic nervous phenomena, and the tendency to crises which may terminate in death." This conception applies to exophthalmic goiter of children as well as of adults.

The cause of exophthalmic goiter is not known. It is probable that the clinical picture is caused by an alteration in amount and character of the thyroid secretion. Disturbances of the sympathetic nervous system, constitutional predisposition, heredity, infectious diseases and nervous shock and stress may be contributory factors, but none of these alone or in combination can be considered as the fundamental cause of the disease.

There are no statistics available which indicate the frequency of exophthalmic goiter in the general juvenile population. At The Mayo Clinic, of 15,505 cases of exophthalmic goiter, slightly more than 1 per cent occurred among children aged fourteen years and younger. According to sex, the ratio of cases among female children to those among male children, as stated by different authors, is from 10:1 to 3:1. In our series of cases this ratio was 7.3:1. The disease may occur at any age. In children the frequency increases from birth to puberty.

Exophthalmic goiter in a child usually develops slowly, but its onset may be acute. In by far the largest number of cases the first symptom is nervousness. Next in frequency are goiter and exophthalmos. Tachycardia and tremor, although less frequent as initial symptoms, are usually noted before the disease has been present for a long time. Weakness, emesis, polyphagia, palpitation, loss of weight, dyspnea, diarrhea, excessive perspiration and intolerance to heat complete the symptom complex, and eventually become evident in a well developed case. In children the objective signs such as nervousness, goiter, exophthalmos, polyphagia, diarrhea and loss of weight may be present for some time before the child complains of the subjective manifestations such as weakness, palpitation and dyspnea.

Enlargement of the thyroid gland is one of the most constant and earliest developments. It is usually bilateral and symmetrical, and usually involves the isthmus. The enlarged gland is firm. The enlargement is painless, and palpation elicits little or no tenderness.

Visible pulsations, palpable systolic thrills and audible bruits may be present over the arteries, particularly those of the superior poles. Since thrills and bruits may also be present

in cases of diffuse colloid goiter, their presence should not be depended on in making a diagnosis of exophthalmic goiter.

Local effects from enlargement of the thyroid gland are not as prominent as in adults. There may be a feeling of pressure in the neck, slight dysphagia or rarely hoarseness from involvement of the recurrent laryngeal nerve.

Tachycardia is present in practically all cases. In 98 per cent of cases the pulse rate was found to be 90 beats or more per minute, and in 80 per cent of cases it exceeded 120 beats per minute. In an appreciable number of cases it is excessive, ranging from 160 to 180 beats per minute. If any doubt exists regarding the influence of extraneous factors, such as excitement, as a possible cause for the tachycardia, the pulse rate should be determined while the child is asleep. If the rate is normal in sleep, the child probably does not have exophthalmic goiter. Palpitation is common, but children do not complain of it early in the disease, probably because they are less accustomed to interpret subjective sensations than are adults.

Evidence of cardiac embarrassment is frequently manifested as dyspnea. This is usually mild, but may be so severe as to constitute one of the chief complaints.

Cardiac dilatation and valvular insufficiency are of sufficient degree to be clinically demonstrable in about half of the cases. Their presence is indicated by expansive movement of the precordium, extension of the borders of the heart beyond normal limits, location of the apex beat well outside the nipple line, and systolic murmurs which are most frequent at the base of the heart.

The characteristic change in the blood pressure consists of an elevation of the systolic pressure and consequent increase in pulse pressure. In 75 per cent of 138 cases the systolic blood pressure was higher than 120 mm. of mercury, and in 68 per cent of the cases it ranged from 120 to 190 mm. of mercury. The height of the diastolic pressure is little affected. The mean pulse pressure in 130 cases was 63 mm. of mercury. Under basal conditions both the systolic and diastolic pressures are lower, but there is no appreciable decrease in the pulse pressure.

Nervous phenomena are the outstanding symptoms of exophthalmic goiter in children. They consist chiefly of excessive

movements and emotional instability. The excessive movements frequently simulate those of chorea and have led to erroneous diagnosis. They may be distinguished from the movements of chorea by their purposeful character. The child becomes restless, fidgety, difficult to control and he picks or pulls at clothes, toys, books and other objects. The disposition of the child may change from one that is quiet, reasonable and friendly to one that is excitable, irritable and fussy. Crying, quarrelsomeness, impatience, fury and rage may be exhibited. The child becomes unable to get along with the family and playmates. Changes in behavior may be so marked as to simulate a psychosis. Schoolwork becomes difficult and often has to be discontinued. Such nervous manifestations as these mentioned here may be expected in all except the milder cases.

Tremors, either fine or coarse, occur in a large majority of cases, and are likely to be exaggerated by voluntary effort. Other subjective nervous phenomena are increased speed of reflexes and flushing of the skin.

Exophthalmos, usually bilateral, but occasionally unilateral, is the most frequent, important, and striking ocular sign of exophthalmic goiter in children. It occurred in 83 per cent of cases. Its presence should always suggest the probability of exophthalmic goiter. Whether or not exophthalmos is present, the eyes may impart to the countenance a staring expression which by some is thought to be even more pathognomonic of the disease than is exophthalmos. This "stare" may disappear as the disease is controlled, although the exophthalmos may persist in gradually lessening degree for a long time. Frequent winking, inability to cause the eyes to converge, lagging of the upper lids as the eyes follow an object describing a downward course, widening of the palpebral fissure and wrinkling of the forehead and raising of the eyebrows when looking upward are ocular signs of secondary diagnostic importance. Edema of the eyelids is found in almost all cases in which exophthalmos is present. Paralysis of the extrinsic muscles of the eyes occurred only rarely in the series of children seen at the Clinic.

General weakness and easy fatigability are present in the majority of cases. The loss of strength is general and often is severe. As a criterion of loss of muscular strength, testing the quadriceps muscle is done most commonly. The child is



asked to step up on a chair. If exophthalmic goiter is present, the effort is attended by unsteadiness, a jerky, uncertain, upward motion, and a tendency to assist in the act by use of the hands. The unaffected child carries out the maneuver steadily, smoothly and without apparent effort. The test was found positive on slightly more than 50 per cent of 157 children who had exophthalmic goiter.

Loss of weight, in spite of an enormous appetite and the ingestion of large amounts of food, is almost pathognomonic of the disease in its early stages. The loss of weight is usually moderate or severe, and in 60 per cent of cases was so marked as to be noticed by the parents. In the later stages the thyroid intoxication may cause loss of appetite, nausea, vomiting (crisis) and consequent rapid loss in weight.

A gain in weight, in the presence of active exophthalmic goiter, may follow a period of rest, especially when this is combined with administration of iodine.

Polyphagia, which was present in 60 per cent of 157 cases, is prominent in the early stages of the disease. Late in the disease the appetite lags, and ingestion of adequate amounts of food is accomplished only with difficulty.

Spells of vomiting, diarrhea or both occur in about a third of the cases. A tendency to looseness and frequency of bowel movements may persist throughout the course of the disease.

The episodes of emesis and diarrhea may be only a part of the picture of crises of exophthalmic goiter, which is made up of fever ( $100^{\circ}$  to  $104^{\circ}$  F.), emesis, diarrhea, increased severity of the nervous and mental phenomena, prostration and sometimes death. Crises are less frequent and less severe among children than among adults. They occurred in 30 per cent of the cases of children in the Clinic series.

Although fever is not a symptom of exophthalmic goiter, there is excessive sweating and a subjective sensation of heat in a large proportion (68 per cent) of cases. This results in so-called "heat tolerance," the desire to do with fewer clothes, and the expressed preference for cool or winter weather. The skin may have an hyperemic appearance caused by the peripheral vasodilatation.

Alopecia occurs in some cases. The nails may be thin, wrinkled, furrowed or undermined.

Edema of the lower extremities may be found in the moderately severe or severe cases. The edema of the eyelids has been mentioned.

The most important laboratory aid in the diagnosis and treatment of exophthalmic goiter is determination of the basal metabolic rate. Boothby and his associates recently have established a new standard for basal metabolic rates which has been named "The Mayo Foundation Standard." The need for such a new standard has been particularly great for the determination of the basal metabolic rates of children. The data on which this standard has been constructed and the manner of its use may be found by referring to the published reports of Boothby and his associates. In children less than six years of age, only a closed room or box type of apparatus can be used, such as that described by Talbot. By the older DuBois standard the basal metabolic rates of seventy children who had received no previous medication with iodine ranged from 0 to +100. The mean metabolic rate in this group was +42. In a group of fifty children, who had received an appreciable amount of iodine previous to the determinations, the values ranged from -20 to +80, but the mean value was +33 as compared to a mean value of +42 in the group of children who had not received iodine. In eighty-one cases, after intensive treatment with iodine, the rates ranged from -40 to +80, and the mean value for the group was +21.

It is evident, therefore, that the basal metabolic rates of children who have exophthalmic goiter tend to be reasonably high (+42). It is further evident that by means of iodine the basal metabolic rate can be decreased to approximately half of the admission rate. This decrease in the metabolic rate by means of iodine has made it possible to carry out lobectomy or subtotal thyroidectomy without preliminary ligation of blood vessels or injection methods of treatment, and has resulted in a lower mortality in spite of the fact that much more formidable types of operation have been carried out.

Lymphocytosis and occasional glycosuria are the only important findings in the blood and urine.

Cases of frank exophthalmic goiter, in which exophthalmos, tachycardia, nervousness and enlargement of the thyroid gland are observed, offer no diagnostic difficulty. As Helmholtz

pointed out, the combination of enlargement of the thyroid gland and nervousness in a child should give rise to strong suspicion of exophthalmic goiter. Undue attention to certain features has led to diagnostic errors. The excessive movements, although not purposeless in character, have led to a diagnosis of chorea. The findings of tachycardia, dyspnea, cardiac enlargement, heart murmurs and elevated systolic pressure have resulted in a diagnosis of heart disease. Asthenia and loss of weight have been ascribed to infection although other signs of exophthalmic goiter were present.

The finding of an elevated basal metabolic rate to  $+30$ ,  $+40$  or more in a child is a strong indication of exophthalmic goiter, even in the absence of such signs as exophthalmos, stare, dyspnea and tremor.

According to H. S. Plummer, a favorable response following the administration of iodine, that is, a decrease of nervous phenomena, is the most valuable test available in the diagnosis of mild cases of exophthalmic goiter.

Exophthalmic goiter in children tends to be progressive. The longer the disease is present, the more deleterious is its effect on the organs and the body as a whole. Complete disability may develop within a year and death may take place in a crisis or from intercurrent infection or other complications. The use of iodine has greatly reduced the death rate, and pre-operative and postoperative crises following its use have become much more rare. In our experience it has permitted more extensive initial surgical treatment, and has reduced the surgical mortality in exophthalmic goiter of children from 9 to 2.5 per cent.

Occasionally mild exophthalmic goiter of children may be satisfactorily treated without resort to operation. In eight cases encountered at the Clinic the disease was successfully controlled by the use of iodine and reduction of activities.

In 97 per cent of 120 glands removed from children with exophthalmic goiter, the essential change was found to be diffuse parenchymatous hypertrophy and hyperplasia. The cells of the follicular epithelium were found to be high cuboidal or columnar, rather than low cuboidal, the type of cell characteristic of the normal gland. The epithelium revealed, as evidence of overgrowth, infoldings or papillary projections into

the lumina of the follicles. In the glands removed from patients who have received iodine previous to operation, the parenchymatous hypertrophy is usually less marked than in the glands from those who have not received iodine. Occasionally additional features, such as thyroiditis, degenerating colloid adenomas, and areas of hemorrhagic degeneration may be found.

The cause of death in uncomplicated cases of exophthalmic goiter is difficult to name. The very common finding of an enlarged thymus and hyperplastic lymphoid tissue, which have been invoked as an explanation of a predisposition to sudden death from obscure reasons, seems to be more likely a result rather than a causative factor of the disease.

There is no known method to prevent the occurrence of *exophthalmic goiter*.

The aim of treatment of exophthalmic goiter should be the reduction of activity of the thyroid gland to a degree that will permit the function of the body and its organs to return to as nearly normal as possible. This occasionally can be achieved by medical methods, although in most cases a portion of the gland should be removed.

In cases of short duration, with a mild degree of activity, rest and Lugol's solution (compound solution of iodine) may be employed under the guidance of frequent and regular determinations of the basal metabolic rate. Activities should be restricted and excitement and overfatigue avoided. From 5 to 10 drops of Lugol's compound solution of iodine should be given three times daily. This regimen must be continued for several months, and in some cases for years. The diet should be the same as that for a healthy, active child, only it should be more liberal in amount.

In cases in which marked cardiac decompensation associated with edema is present, digitalis can be used to good effect. One c.c. of the standardized tincture may be administered daily, but the administration should be discontinued for a week or ten days before surgical measures are carried out.

The use of sedative drugs is seldom if ever indicated, in view of the striking effect of iodine on the nervous phenomena.

In a considerable number of cases the use of the roentgen rays or radium for children was followed by no improvement

and in some, the condition of the children became worse, although subsequently surgical intervention was productive of marked benefit.

Following a preparatory period of two to four weeks, during which 10 drops of compound solution of iodine is given three times a day, resection of the greater portion of both lobes of the thyroid gland can be carried out with a high degree of safety. The improvement which follows this procedure usually amounts to a cure. Administration of iodine is to be continued throughout the postoperative course, and sometimes for months or years following operation. Postoperative myxedema, which is rare in children, necessitates the administration of desiccated thyroid. We have not encountered postoperative parathyroid insufficiency in any children in the Clinic series of patients.

#### HYPOTHYROIDISM

**Cretinism.**—Insufficient thyroid secretion may be manifested in children as athyreotic cretinism, endemic cretinism or myxedema. The term "athyreotic cretinism" is used here to designate the condition resulting from partial or complete failure of development of a functioning thyroid gland in the fetus during intra-uterine life. Synonymous terms are "sporadic cretinism" and "athyreosis." The term "endemic cretinism" is employed to designate a congenital hypothyroid state in an individual born of parents from so-called "endemic goitrous districts," and one or both of whom suffer from congenital insufficiency of thyroid secretion. Synonymous terms are "congenital cretinism," "congenital myxedema" and "congenital hypothyroidism." The chief points of distinction are: (1) in athyreotic cretinism the patient does not suffer from lack of thyroid secretion before birth, whereas in endemic cretinism, patients are deprived of sufficient secretion probably throughout their entire intra-uterine life, and (2) athyreotic cretins are born of normal parents, but endemic cretinism results from hereditary thyroid insufficiency. As endemic cretinism is rare in this country, this discussion will be limited to athyreotic cretinism as it occurs in this country, and for the sake of brevity the term "cretin" will be used to indicate an athyreotic cretin as opposed to one suffering from endemic cretinism.

Although the condition is congenital its recognition may be delayed until the child is several weeks or months old. Failure of development of the thyroid gland occurs in spite of the fact that the parents are free from disease of the thyroid. Contrary to the situation regarding endemic cretinism, there is no proof that lack of iodine in the diet of the mother is responsible for the occurrence of athyreotic cretinism.

Cretinism is caused by lack of thyroid secretion. Since the infant is protected by the maternal thyroid secretion, it does not suffer from this lack of secretion during intra-uterine life, and therefore it appears normal at birth. The patient who has endemic cretinism, on the other hand, shows the effects of intra-uterine deprivation of maternal thyroid secretion.

Following birth, insufficiency of thyroid secretion becomes manifest at the age of a few weeks. The infant, although normal in size at birth, fails to grow at the usual rate. The body remains short and appears well nourished. The extremities are short and pudgy, the face is round, and the features are coarse and heavy.

The skin is dry, thick, wrinkled and cool. The skin over the forehead is wrinkled transversely and gives the appearance of redundancy. The hair is sparse, coarse, dry and brittle. The eyebrows are scanty or absent. The complexion is pasty. The eyes are dull, and the expression is sleepy and apathetic. The base of the nose is broad, the nostrils are large and patent, the lips and tongue thick, the latter often partly protruding. Drooling is excessive. The tissues of the lids and face are full and thick, suggesting edema. The chin is short and recessive. The ears project unduly from the sides of the head.

The neck is short and broad and the head is maintained in poor position. The thyroid gland is usually not palpable. Rarely, thyroid enlargement is present. In endemic cretinism, on the other hand, goiter is almost a constant finding.

The chest and abdomen are short, thick and heavy. The musculature of the abdominal wall is relaxed, the abdomen is protuberant and an umbilical hernia is almost invariably present. When the child is in the erect position, marked lordosis is evident. Above the clavicles are the thickened "myxedematous pads" which fill the angles between the neck and supraclavicular region. The extremities are short, the hands

are spatulous and thick. The external genitalia remain infantile, and in the male the testes are frequently undescended.

Roentgenographic examination of the skeleton is an aid in diagnosis. The cartilaginous condition of the growing portion of the bones persists beyond the usual length of time. The fontanels and sutures of the cranium fail to close. Dentition and the shedding of deciduous teeth are delayed. Centers of ossification are tardy in developing, or fail to develop. Unusual delay in the appearance of centers of ossification of the carpal bones frequently indicates a lack of thyroid secretion.

The infant with cretinism is usually quiet and inactive. The appetite is poor. The speed of tendon reflexes is reduced: the knee jerk may appear active, but return of the leg to the position present before elicitation of the jerk is characteristically slow.

Physical and mental development are markedly retarded. The special senses give evidence of decreased acuity. The ability to sit erect, to walk, and to talk is slow to appear. The gait is wobbling. Speech is slow, inarticulate, and guttural, and the vocabulary is limited. Control of the bowels and bladder develops late, or not at all. Mental progress is practically nil, so that the ultimate status is one of idiocy.

All of the physiologic processes of the body are depressed. The temperature is subnormal; the pulse and respiration are slow. The intake of food and fluid is small, and the output of waste products is decreased. Constipation is marked. Albuminuria and cylindruria are commonly noted. Secondary sexual changes fail to take place. The blood picture is comparable to that found in infants. There is a leukopenia and relative lymphocytosis. The basal metabolic rate is greatly reduced, usually to  $-40$ , or even lower. Hypoglycemia and increased glucose tolerance are usually present. The blood cholesterol may be elevated.

The thyroid gland in cretinism is atrophic or absent. The finding of round-cell infiltration in the aplastic gland of cretins has been accepted by some investigators as evidence of fetal thyroiditis.

Early recognition is of paramount importance, since the longer the delay before treatment, the more extensive become the permanent and irreparable changes. In infants particu-

larly, the condition is likely to be erroneously diagnosed. Mongolian idiocy is frequently miscalled "cretinism," but the mongol is active and more interested in his surroundings, and the condition, unlike cretinism, is evident at birth. Infantile cerebral palsy can be distinguished from cretinism by a history of trauma or infection, by the marked muscular incoördination, spasticity, and irritable central nervous system. Physical and mental retardation of all types can be readily distinguished from cretinism by a therapeutic test with thyroid substance, which if properly carried out, will result in no harm.

The outlook in cretinism depends on the age at which treatment is inaugurated, and the thoroughness and continuity with which it is carried out. Although physical growth and development may attain that of the average child, mental development tends to lag, and only in the cases in which treatment is begun early can the mentality be expected to parallel an apparently normal physical status.

Untreated cretins or cretins for whom treatment is greatly delayed, develop the characteristics enumerated in the foregoing, and even if belated treatment is given them, they remain markedly retarded both physically and mentally. The mental state of such individuals is that of idiocy, and they become subjects for institutional care.

The first essential for proper treatment is to be certain that the thyroid preparation to be used is potent, and the potency must be relatively constant. Cretins have been treated for months and even years with preparations of thyroid which were capable of exerting little, if any, beneficial effect.

Adequate dosage must be determined for each child. For infants and young children whose basal metabolic rates can be obtained only with great difficulty, the condition of the child must serve in most instances as a guide. The rapid improvement during the first week or two of administration of thyroid extract may be followed by evidences of overdosage, such as irritability, tachycardia, continuous loss of weight, diarrhea and sweating. The appearance of such phenomena is an indication for reduction in the amount of thyroid extract given. A return of even mild degrees of previously existing signs warrants an increase to an amount that is somewhat less than that



of the original dose. As growth progresses, slight increases of  $\frac{1}{8}$  to  $\frac{1}{4}$  grain (0.008 to 0.016 gm.) may be made.

The requirement for thyroid extract varies. As a rule, from  $\frac{1}{2}$  grain to 2 grains (from 0.032 to 0.12 gm.) of desiccated thyroid, as marketed by the dependable pharmaceutical houses, will suffice to maintain the metabolism at, or near, normal. Larger and frequent changes in the dose should be avoided, and in no instance should the treatment be completely eliminated.

In all the cases encountered at the Clinic, one standard preparation of desiccated thyroid has been used, and for this preparation, on the average,  $\frac{1}{4}$  grain (0.016 gm.) daily has been found about the proper amount for infants,  $\frac{1}{2}$  grain (0.032 gm.) daily for children between one and three years of age,  $\frac{3}{4}$  to 1 grain (0.05 to 0.065 gm.) for children between three and five years of age, whereas older children and adults are usually maintained on 1 to 2 grains (0.065 to 0.12 gm.) a day. Children often appear to need slightly more in proportion to their size than adults.

**Myxedema.**—Myxedema in infancy and childhood is a disease dependent on a decrease in amount of thyroid secretion, which begins after birth.

The terms "infantile," "childhood" and "juvenile," as applied to myxedema, indicate the period of childhood at which the decrease in thyroid secretion begins. It is implied that a child in whom myxedema develops has been normal for months or years before the onset of trouble, thus differing from cretinism in which thyroid deficiency is present at, or before, birth. The term "congenital myxedema" is employed by some in a sense equivalent to either "athyreotic cretinism" or "endemic cretinism." Gull's disease (spontaneous myxedema of adults), and "cachexia strumipriva," the term suggested by Kocher to designate the condition which follows complete removal of the thyroid gland, have been thought of as applying to adults only, although both spontaneous (idiopathic) and postoperative myxedema occur among children.

Infection and trauma have been ascribed rôles in the production of myxedema of children. In some cases the onset occurs after a febrile illness. Operative procedures on the thyroid gland occasionally result in myxedema of children. In

most cases of myxedema of infants and children, the factor or factors responsible for degeneration and suppression of function of the thyroid gland are not known.

The condition is relatively rare among children. It may occur at any period of childhood, and is said to be more frequent among girls than among boys.

The clinical picture varies considerably, depending on three factors: (1) the age of the child at the time of onset; (2) the duration, and (3) whether or not the remnants of the thyroid gland can still produce and give off traces of thyroxin. The onset is usually gradual. Attention is called to the condition chiefly because of arrested growth, or because of arrested, or decreased, mental development. In general, it may be said that in all cases the condition tends to approach that noted in examination of untreated cretins, but cretinism is prevented because of the onset later in life, thus allowing time for more complete development of the various organs of the body. The length of time required to produce the complete picture of myxedema, after complete cessation of thyroid function, is between six and eight weeks. Gradual cessation of function would of course prolong the development of the complete picture.

The child who has myxedema of long standing is of shorter stature than the average. The head is large, the trunk short and thick, the extremities stubby and the hands spatulate.

The face is round and pale, and the complexion pasty. Deposits of nonpitting myxedematous tissue, especially noticeable in the lower lids, impart an appearance frequently mistaken for that of nephritis or nephrosis. The features become coarse, the lips thick and the expression becomes dull. Often these changes are of minor degree only, and although they should be the first indications noted, frequently they are overlooked.

The skin becomes dry, rough and scaly. Myxedematous deposits are characteristically noticeable in the supraclavicular fossæ, the tissues of the face, or in any other part of the body. The hair becomes scanty, the eyebrows and eyelashes may be lost and even alopecia may appear. The child becomes sensitive to cold and prefers warm clothes and warm surroundings.

Bodily movements become slower and incoördinated. Run-

ning and jumping are discontinued, and the child walks or sits quietly more than usual. Interest in play and schoolwork and in the surroundings generally lags. Speech becomes slow and thick, and response to questions is delayed. The voice assumes a lower pitch and becomes hoarse and guttural. The disposition is usually quiet, placid and unexcitable.

The pulse is slow. The body temperature is reduced. The appetite may remain fair or it may decrease to a marked degree. In spite of this, the weight may temporarily increase, on account of the accumulation of subcutaneous myxedematous deposits. A tendency to constipation may appear.

The clinical picture is reflected in the characteristically lowered metabolic rate. This, as a rule, reaches a level of from  $-25$  to  $-35$ , although figures above and below these have been obtained. In cases in which there is complete loss of thyroid function, the level is usually from  $-35$  to  $-40$ .

If the disease has persisted for some time before the child comes under the observation of a physician, a roentgenogram will reveal the characteristic persistence of the cartilaginous synchondroses and delay in ossification. Although less striking than in cretinism, the evidence so elicited may be equally informative. Centers of ossification in the carpal bones may be present in number consistent with the age of the individual, but the lack of full extent of their development indicates arrested growth.

The urine may contain albumin. The phenolsulfonphthalein test may give evidence of decreased renal function. The urinary excretion of nitrogen is low because of low intake of food and the tendency to a positive nitrogen balance as the edema is developing.

Secondary anemia is common. The blood sugar level is elevated. The glucose tolerance often is increased. Values for blood cholesterol usually are elevated.

Difficulties and errors of diagnosis are more common in the less severe cases. Confusion with nephritis has been mentioned. The delayed growth has been ascribed to rickets, achondroplasia, and chondrodystrophy. Designation of cases of infantile myxedema as cases of cretinism constitutes more a confusion of terms than an error in recognizing the underlying disorder. The most frequently made error is the com-

plete overlooking of cases of slowly developing myxedema in older children. Resort to determinations of basal metabolic rate and to roentgenologic study of the growing portions of the skeleton will serve to clear up the diagnosis in doubtful cases.

The outlook for life is usually good. Children who have myxedema live for a long time but are subject to handicaps of varying degrees. A child who suffers from myxedema for any considerable time cannot be restored to a completely normal state, for just as in the case of cretinism, if a major part of the period of life intended for growth is lost, it cannot be replaced. In cases in which mentality has not been interfered with, physical growth can be stimulated, but not to such an extent as to supply average stature by the time maturity is attained. Disappearance of other symptoms is to be expected if the patient is under proper management, but the end-result will be an individual who is less than normal in stature, or below the average of intelligence, or both, unless recognition of the disease is early and treatment is promptly instituted. Severe, untreated myxedema of children who are less than two years of age have much the same outlook as that of untreated cretins, that is, idiocy. On the other hand, if the condition is recognized early and the children are appropriately treated throughout life they should, as a rule, be practically normal in all respects.

The thyroid gland is small, atrophic, and fibrous. The vesical walls may be the seat of round-cell infiltration.

The same principles of treatment are employed as in cretinism. In both conditions one of the first and most important duties of the physician is to explain fully to the parents, and also to the child as soon as he is old enough to understand, the full significance of the disease and that the patient must take a potent thyroid preparation throughout his life. He must be impressed with the fact that he should never miss taking medication even for one day, and must always plan to have on hand an ample supply of the thyroid preparation on which he has been standardized. There is no disease more satisfactory to treat and in which treatment is more certain of success if the proper principles of treatment are followed throughout life.

## INFLAMMATION

Acute inflammation of the thyroid gland is rare. It is possibly more common among children than among adults, probably because the etiologic agents are more often present in the young.

It occurs more frequently among females than among males. As it tends to affect goitrous thyroid glands more often than normal glands, it is obvious that females, with their higher incidence of goiter, would likewise be more frequently subject to acute thyroiditis.

Many, and perhaps most of the diseases of bacterial or protozoal etiology may be accompanied by thyroiditis. Infections by staphylococci, streptococci, *Eberthella typhi* and *Salmonella paratyphi*, pneumococci, *Hæmophilus influenzae* and *Corynebacterium diphtheriae*, as well as filtrable viruses, may give rise to acute thyroiditis. Trauma may play a part. The organisms reach the gland in most cases by way of the blood stream.

In nonsuppurative forms there is a diffuse leukocytic infiltration of the organ, with proliferation and desquamation of the epithelial cells. In the suppurative form, congestion, abscesses, hemorrhage, liquefaction, and even gangrene of a part, or of the whole, of the gland may be found.

The onset is usually rapid, with chills and fever. Pain, which is increased by swallowing, and swelling of the gland, which is firm at first but which becomes soft over regions of suppuration, are the chief features. Dyspnea, cough, alteration of the character of the voice, and tachycardia may be present.

The history of preceding illness, evidence of acute infection such as fever, leukocytosis, and local pain, swelling, and tenderness are the chief features on which the diagnosis rests.

The outlook is uncertain. Mild conditions subside, but in severe cases, in which there is suppuration, the disease may be fatal, or there may be such a widespread destruction of tissue as to result in myxedema.

Application of heat to the region of the gland may serve to prevent spread of infection to surrounding parts. If suppuration occurs, surgical drainage becomes necessary. If myxe-

dema results, treatment by means of thyroid preparations becomes necessary.

**Chronic Thyroiditis.**—The thyroid gland may be involved by miliary tuberculosis and by congenital syphilis. Such cases are interesting from the pathologic standpoint, but constitute little of clinical importance.

Riedel's disease is of very rare occurrence among children. Riedel reported one case in a child, aged four years. It is characterized by a very firm gland which, on section, reveals extensive fibrosis, some evidence of epithelial proliferation, and collections of inflammatory cells of various types. A hard, firm swelling, pain, dyspnea, and dysphagia are the chief symptoms, and are usually interpreted as indicating malignancy. Treatment is surgical.

#### MALIGNANT DISEASES OF THE THYROID

Malignant diseases of the thyroid are not of common occurrence among children (Fig. 41). In the past twenty-five



Fig. 41.—Adenocarcinoma (grade 1) in the thyroid gland of a girl aged seven years. It is not possible to distinguish such a malignant nodule from a benign adenoma without removal and pathologic examination

years only seven cases of malignancy of the thyroid were found among children admitted to the Clinic.

Malignancy in the thyroid may have its onset early or late in childhood. The first manifestation is an irregular, firm swelling of a portion or of the entire thyroid gland or of the adjacent lymph nodes. Dyspnea, more marked on exertion, is the chief subjective complaint. There is little, if any increase in the metabolic rate, but there may be some evidence of hypofunction of the gland. The neoplasms are adenocarcinomas of low degrees of malignancy. All of those seen at the Clinic were graded 1 and 2 according to Broder's system of grading malignant tumors. The diagnosis can be established by examination of a portion of the mass, or of an adjacent lymph node.

The disease is only slowly progressive, and the life expectancy is a matter of years rather than of months.

Surgical removal when possible, and subsequent irradiation with roentgen rays comprise the most satisfactory forms of treatment for these patients.





## TULAREMIA: DIAGNOSIS AND TREATMENT

THOMAS B. MAGATH

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ALTHOUGH tularemia has been studied as such but little more than a decade, more is known about the causative organism, its transmission, the lesions it produces, the symptoms it causes, and about the prophylaxis, treatment, and incidence of the disease, than practically any other infection.

When the disease was known only in the western states, the difficulties of diagnosis were restricted; but now that it has been reported from every region of the United States, many parts of Canada, and from other continents as well, geographic factors no longer serve to prod the clinician's threshold of suspicion; he may encounter the disease in a patient from any locality.

### DIAGNOSIS

The occupation of the patient is important. If he is one who by the nature of his work must handle wild game, or ride the western or middle-western prairies or farm land, he is more liable to contract tularemia than otherwise; and if he is a hunter who bags and skins his own game, he is also liable to infection. Men are much more often infected than women, but women who clean and cook rabbits and certain other game are also liable to become infected.

Of fundamental importance in the diagnosis of tularemia is the history of contact with one of the susceptible mammals, birds, insects or ticks. While it is by no means certain that all the transmitting agents have been discovered, it is known that the disease is naturally present in the wild rabbit, grouse, coyote, cat, fox, muskrat, squirrel, woodchuck, range sheep, meadow mouse, rats and horned owl. Wilbur and Leser recently reported a case contracted from handling a ringneck pheasant. Insects known to transmit tularemia are the deer

fly (*Chrysops discalis*), the wood ticks (*Dermacentor andersoni*, *Dermacentor variabilis*, and *Dermacentor occidentalis*), the rabbit tick (*Hæmaphysalis leporispalustris*), and the grouse tick (*Hæmaphysalis cinnabarina*). Failing to elicit the history of contact with one of these mammals or birds, as by handling, dressing, cooking, or caring for their pelts or skins, or of being bitten<sup>1</sup> by one of these insects or ticks or by contact with the body juices of such insects, as by slapping the insect and spattering its contents into the eye, one must inquire into the possibility of the patient's having handled cultures of the organism or experimented with animals inoculated with *Pasteurella tularensis*.

The history of contact with a valid source of infection is so important that the possibility must be thoroughly explored and, failing to obtain a positive history, the probability of tularemia must be only remotely considered.

**The Lesions.**—The time of the appearance of the local lesion after exposure is significant and, as a rule, is from one to four days, rarely as long as twelve days. A limited group of cases have been reported in which no local lesion occurred and these, for the most part, have been among laboratory workers. Although, experimentally, the organism can be made to invade the body through the unabraded skin, it has been suggested that the so-called typhoidal type of tularemia occurs as a result of accidental ingestion or insufflation of the organism. Occasionally one may swallow a tick and, if infected, it might conceivably cause the disease.

The location of the lesion is most frequently on the hands or arms, but lesions of the eye are by no means uncommon. If the disease is acquired from ticks, the location of the initial lesion might be any place on the body, but it is most often on the lower extremities.

The lesion begins as a papule, and by necrosis an ulcer forms during the second week. Such ulcers are of the punched-out type with diffuse necrosis, polymorphonuclear cell infiltration and nuclear fragmentation; the ulcers break down early and drain. There is an early (often in forty-eight hours) lymphangitis and lymphadenitis, affecting the regional lymph

<sup>1</sup>Some have suggested the bacteria are transmitted by the feces of the tick and not by its bite.

nodes. These are tender and painful and usually proceed rapidly to suppuration.

The general symptoms, which begin abruptly, are like those of any other severe infection. The fever curve shows an abrupt rise, often to  $103^{\circ}$  or  $104^{\circ}$  F., and remains at a high level with but slight fluctuations. There are often distinct periods of remission followed by recurrence of the fever. After two weeks or a month of such bouts the fever usually subsides, but the symptoms of fatigue and even prostration continue for some time, even for a year.

Not uncommonly one observes physical and subjective signs of bronchitis, bronchopneumonia or even pleural effusion, and indeed these may be very prominent. In certain cases in which no local lesion is found the whole course may be one of bronchopneumonia. In some cases without local lesions the disease simulates typhoid fever, and in any particular case leukocytosis, enlargement of the spleen and skin lesions, such as macules, papules, vesicles and pustules, may occur.

#### LABORATORY FINDINGS

The laboratory investigation of tularemia is of paramount importance. If the patient is observed during the first two weeks of the infection, one may be successful in isolating the organisms from the lesion either by culturing on cystine agar, as recommended by Frances, or by modification of this medium, as proposed by Rhamy and by Foshay. The organism may also be isolated from a draining lymph node or from the blood stream. One is more likely to succeed if a guinea-pig is first inoculated with the material to be tested. Within five or six days the animal will show the typical lesions, from which *Pasteurella tularensis* can be readily obtained if the organism is present in the material. *Pasteurella tularensis* is a gram-negative, nonmotile, pleomorphic bacillus, growing scantily as a rule. It ferments glucose and glycerol, and most strains ferment mannose, levulose and maltose. In the presence of these sugars, acid is first produced, then alkali. Hydrogen sulfide is produced by its action on cystine.

**Skin Test.**—A skin test developed by Foshay is reported to be very useful and reliable in the early diagnosis of the disease, in fact, as early as the third day after infection. The

antigen is prepared by killing and treating a suspension of bacteria with 1 per cent formaldehyde for twenty-four hours, then treating it with hydrogen peroxide for forty-eight hours, followed by 1 per cent sodium ricinoleate in distilled water for twenty-four hours. The preparation may be made by treating organisms with nitrous acid for twenty-four hours, then suspending them in 1 per cent sodium ricinoleate and treating with 0.5 per cent phenol. If the disease is of recent origin, a test is made by injecting a small amount of antigen intracutaneously, enough to make a wheal 2 mm. in diameter; if the disease has been present for some time, enough antigen is injected to make a wheal 4 mm. in diameter. When read at forty-eight hours, a positive reaction has an erythematous wheal 5 to 6 cm. in diameter, with a hard indurated center about 1 cm. in diameter. The reaction lasts five days and a brown patch remains for several weeks. The test will be positive at least as long as five years after infection; it must be interpreted, therefore, in light of the patient's symptoms.

**Agglutination Test.**—After the patient has suffered from the disease about two weeks, the blood serum exhibits both a positive complement-fixation reaction and a positive agglutination test.

The complement-fixation test is performed along standard lines using as antigen a suitable suspension of the organism. The test is of scientific interest, but on account of its complexity it is not recommended for routine use. Of greater practicality, the agglutination test is to be preferred. A suitable, killed suspension of the organism is treated with varying dilutions of the patient's serum and the reading is made after incubation. At first the titer is low, 1:40 to 1:80, but it rises rapidly and, by the third week, it is usually quite high, even as high as 1:5,000. The reaction persists for months or even years. A rising titer is perhaps the most perfect corroborating test, next to actual isolation of the organism from the lesion, a very much more difficult task. In cases without a local lesion or exact history of exposure, especially when the chief findings are in the chest, a rising titer in the agglutination test may be the chief basis for establishing a diagnosis.

If one must make the diagnosis at necropsy, it must rest on the finding of typical lesions in the lung, liver and spleen.

miliary necrotic areas, essentially caseous. The lesions in the lungs are characterized by thrombosis of small arterioles with necrosis, and surrounding mononuclear cell infiltration. One may isolate the organism from the lesions; or better, inoculate a guinea-pig with the material. It may be possible to obtain enough serum with which to perform an agglutination test.

### TREATMENT

**Prophylaxis.**—One may fairly successfully avoid the disease by handling no susceptible animals and by avoiding ticks and deer flies. In dressing game, rubber gloves should be worn, and sick wild rabbits, squirrels and mice should be avoided. Certainly after handling any of these animals the hands should be carefully scrubbed with soap and water and washed in an antiseptic solution. If one has received scratches or wounds while handling susceptible animals, the wound should be treated by thorough washing and application of a good antiseptic.

Foshay has advocated immunizing laboratory workers and those engaged in the wild rabbit industry with a detoxified vaccine he has developed, but as yet no extensive use of it has been reported.

**Active Treatment.**—Aside from general supportive measures and surgical drainage of liquefied lymph nodes, there is no particular remedy to advise except certain specific procedures.

In a limited number of cases, two having been reported by Baer, the local lesion has been treated with roentgen rays. Both of Baer's patients were treated before the fourth day; one had lymphadenitis but the other did not, and a positive agglutination test developed in both cases, although at first it was negative. The patients were treated with one-half unit (erythema) of unfiltered roentgen rays applied to the lesion and both showed marked improvement the next day. The disease was apparently aborted.

After the disease has advanced, various forms of treatment have been suggested. Fisher reported treating three patients with neoarsphenamine, although the first case was diagnosed on the basis of the history and clinical manifestations only. Three doses, 0.45 gm., 0.6 gm., and 0.75 gm., were given at five-day intervals. He reported that all the patients were well

after the third dose. Some isolated instances of beneficial results following the use of certain dyes have been reported, but these reports and the lack of confirmation leave one doubtful as to the value of such remedies.

**Foshay's Serum.**—The greatest progress in treatment has been made by Foshay. He has immunized goats and horses over long periods of time with detoxified antigens of *Pasteurella tularensis*. The serum is obtained and administered intravenously, usually in two doses of 15 c.c. each on successive days. In cases in which the lymph nodes are greatly involved, a third dose is indicated. It should be given as early as possible and with the usual precautions against reactions. Improvement is usually noted on the third day. He has reported on 240 cases treated with striking effects. The duration of fever was not shortened, being 26.44 days on the average. The duration of adenopathy was lessened by nearly half, or to 2.41 months. The duration of the disease and the disability due to it was shortened to 2.78 months, or about half the time of untreated cases, and the freedom from subjective symptoms was effected almost immediately. The mortality was reduced to about a third the usual mortality of 6 to 8 per cent.

The best and most striking results are obtained when patients are treated during the first three weeks and, after eight weeks, it is questionable whether the risk of serum treatment and the uncertain benefit to be gained justify its use.

Sharp and Dohme have placed on the market a serum made after the manner of Foshay, and Flinn reported favorably on its use in two cases. One patient was given 30 c.c., the other 90 c.c., followed by 30 c.c. of Foshay's immune goat serum. Since these are the only reports available, one must reserve opinion on the commercial product until more cases are reported. It would be advisable to develop some means of concentrating the serum, as has been done with better known immune serums.

It can be seen that specific treatment of tularemia is still somewhat in an experimental stage, but the brilliant results which have attended work on this interesting infection foreshadow a solution to the problem of treatment in the not too distant future.

## CUTANEOUS MANIFESTATIONS OF SYSTEMIC DISEASE

LOUIS A. BRUNSTING

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A THOROUGH understanding of the structure and functions of the skin is essential to an appreciation of the rôle of this organ in general bodily economy. It is taken for granted that the skin serves as a protective outer coat, but aside from this it is not only the largest, but one of the most vital organs of the entire body. Like the liver, the skin can repair itself to a certain point, but when one-half to two-thirds of its surface is destroyed, as in the case of extensive burns, for example, life is impossible.

Dirt, bacteria and water do not penetrate the unbroken skin by virtue of the protection afforded by the waxy, sulphurous keratin of the stratum corneum. This material multiplies itself in response to friction and furthermore serves as a buffer against undue exposure to ultraviolet light. The pigment of the skin, found in the basal cells of the epidermis and in the chromatophores of the upper cutis, is laid down in response to certain external stimuli, such as light, heat and friction, but it is controlled from within the body through a chemical and nervous mechanism which is little understood.

The several layers of the skin, including the fat, serve as a blanket to check the loss of bodily heat by radiation. On the other hand, the dilatation or constriction of the superficial capillaries and the evaporation of sweat are important factors as well in temperature control. No small amount of sodium chloride is excreted in the sweat in prolonged febrile bouts such as in malaria, pneumonia or artificial hyperpyrexia.

The subcutaneous tissues serve as a spongy reservoir for the storage of water and excess nourishment in the form of glucose, and these are held until they are needed elsewhere.

The reticulo-endothelial system in the skin is significantly associated with immunologic phenomena, tests for susceptibility to tuberculosis, scarlet fever, diphtheria, tularemia, lymphogranuloma inguinale and fungous infections being interpreted by intracutaneous tests. Likewise, the skin is a shock tissue in certain anaphylactic phenomena, and tests for protein sensitization in asthma, hay fever, eczema, and so forth, utilize the urticarial reacting mechanism of the skin.

Undoubtedly the skin is the medium which adapts the vitamins activated by the sun to the use of the body, perhaps by means of active irradiation of sterols in the epidermis; the exact mechanism of this process of transfer, however, is not known.

Disorders of the skin comprise too complex a subject to be adequately discussed except in a textbook. There are common diseases which are entirely limited to the skin alone, such as moles and new growths (both benign and malignant), parasites, and infections by fungi and other microorganisms; and there are lesions which appear on the skin but are really the expression of an underlying constitutional disturbance, such as tuberculosis, syphilis, or lymphoblastoma. In this latter sense the skin may be thought of as a mirror that reflects the state of the general health of the body. The study of the skin and its disorders from this point of view is the intriguing feature of the science of modern dermatology.

#### DISORDERS OF PIGMENTATION

**Addison's Disease.**—The cardinal symptoms of Addison's disease are asthenia and a gradual decline in general weight and strength associated with a uniformly low value for the systolic blood pressure and, in most instances, a generalized pigmentation of the skin which is especially pronounced in the folds of the body, the axillæ, and in the genital and perianal regions. The skin assumes a soft, smooth texture. Hyperpigmentation is the rule, although it may be absent. Usually the mucous membranes are involved as well as the skin. Microscopically there is simply an increase in the amount of pigment in the basal cells and chromatophores where it is ordinarily found. In Addison's disease it happens rather frequently that



pigmentation of the skin is the first sign of the syndrome which calls attention to the correct diagnosis.

**Acanthosis Nigricans.**—This is a rare disease which affects juveniles as well as adults. I am concerned here only with the latter type. Examination of the patient reveals hyperpigmentation of the same sites as those that are involved in Addison's disease, namely, the axillæ and the genital folds most of all, although there is also a permanent exaggerated wrinkling of the skin in these sites which is quite characteristic. One may find small papillomas on the skin of these regions or along the sides of the neck. The microscopic picture is quite distinctive: There is an increased thickness of the stratum corneum, but the most important change is in the prickle-cell layer, where there is a marked amount of irregular acanthosis with adjacent areas of thinning of the skin almost to the point of atrophy. Pigmentation is irregular and is particularly prominent below the zones of acanthosis. The clinical importance of the cutaneous picture of acanthosis nigricans in almost all the cases in which adults are affected is its association with abdominal or pelvic malignancy. Apparently the changes in the skin are secondary to some involvement of the chromaffin-sympathetic system.

**Hemochromatosis.**—Pigmentation in this condition is characterized by diffuse bronzing of the skin, from which it gets the name "bronze diabetes," because there is usually an associated diabetes or some obscure disorder of the liver such as cirrhosis. The demonstration of this iron-containing pigment in the skin by selective staining is usually sufficient to make the diagnosis. It happens most often that biopsy of the skin is necessary in order to settle a puzzling diagnosis in regard to visceral disturbance, the discoloration of the skin rarely being sufficiently diagnostic in itself.

**Other Disorders of Pigmentation.**—The foregoing conditions must be distinguished from certain other disorders which are characterized by pigmentation of the skin. Chronic arsenism resulting from a reaction to the pentavalent and inorganic arsenical preparations, such as potassium arsenite (Fowler's solution), is quite distinctive clinically and histologically. Over the trunk there is a mottled appearance of alternating hyperpigmentation and depigmentation which gives

a raindrop effect. In the same individual one may frequently find discrete hyperkeratoses of the palms and soles which may terminate in malignant degeneration.

Diffusely generalized hyperpigmentation is seen in argyrosis, but the color is more blue-gray than brown and pigmentation is usually a consequence of the ingestion of silver compounds, or their medical use on mucous membranes over a prolonged period. Microscopically, the glistening particles of silver are best demonstrated by dark-field illumination in a lightly stained section where they will be found chiefly in the propria of the sweat glands and in the region of the blood vessels. The use of silver nitrate was formerly in vogue in the treatment of peptic ulcer; today it is only rarely used for this purpose.

In some cases of Hodgkin's disease diffuse hyperpigmentation of the entire skin may occur without other objective evidence of the disease being present. Now and then one sees examples of this condition wherein the pigment is limited to zones or bands along the forehead or on the trunk. Following exfoliative dermatitis from several causes the skin is usually hyperpigmented for many months. In cases of scleroderma of the diffuse type one frequently sees a most intense darkening of the skin, which may be generalized. In women during pregnancy or during the menopause or in the course of thyroid or ovarian disease there may be localized or generalized increases and decreases in pigmentation. The yellowish appearance of the skin in cases of pernicious anemia is well known, as is the chamois color of the xanthomatous individual in whose blood and tissues there is an excess of lipoids. An excess of carotene in the blood resulting from the overuse of oranges, carrots, or certain green vegetables in the diet often stains the skin yellow, which coloration can be detected particularly on the palms and soles. In polycythemia vera the face, neck, and extremities are tinged from dusky purple to brick red. The presence of disease in the gallbladder or liver may first become manifest when the skin and sclera become tinted with bile pigments, producing jaundice. Other discolorations of the skin characterized by hyperpigmentation are familiar to dermatologists, and many of such conditions are the result of local irritation in the skin itself, resulting from infestation with parasites, or neurotic excoriations and so forth, and they must

be differentiated from the foregoing conditions which have to do with systemic disease.

### PRURITUS

No one has satisfactorily explained the symptom of pruritus or the mechanism by which it appears as the presenting symptom of underlying systemic disease. Like pain, pruritus is subjective and varies tremendously among individuals, and on various occasions in the same individual. The most common clinical entity with which pruritus appears is jaundice. Few patients who have had complete biliary obstruction from stricture or neoplasm fail to have some degree of pruritus in association with other symptoms. It frequently happens that pruritus is the earliest symptom before the skin and the sclera become tinted and, in fact, there may be itching of the skin in association with disease of the liver and gallbladder without any elevation of the serum bilirubin or any clinical evidence of jaundice.

Pruritus is usually most intense in urticaria, and it may occur in dermatographism without the presence of wheals. Elderly individuals whose skin and accessory structures are undergoing natural involution sometimes have an intractable pruritus without apparent cause. When this condition affects elderly men, a search should always be made for a disorder of the urinary tract, such as urinary retention from enlargement of the prostate gland with resulting accumulation of excessive amounts of nonprotein nitrogen in the blood. Urticaria is sometimes the first symptom of hyperthyroidism. In diseases such as the lymphadenoses, pruritus and objective changes in the skin occur in more than a third of the cases. When pruritus exists for a considerable time without objective evidence of disease, a careful search should always be made for enlargement of such lymph nodes as can be palpated or that can be detected in the mediastinum by roentgenograms of the thorax. Smears of the blood may point to changes of Hodgkin's disease, or there may be evidence of one form or other of leukemia. Pruritus is rare in cases of lymphosarcoma unless it is associated in its course with one of the other manifestations of lymphoblastoma. In granuloma fungoides, on the other hand, the disease is frequently preceded by a long period of pruritus and by more

or less eczematoid changes in the skin resembling parapsoriasis. In cases of individuals having a background of allergic disease such as asthma and hay fever one encounters paroxysms of pruritus which may become evident on the skin in the form of urticaria or neurodermatitis. In pregnancy and in diabetes a troublesome pruritus may develop, but it is usually of the localized type and affects particularly the perianal regions and the genitals.

#### ENDOCRINE AND METABOLIC DISTURBANCES AND THEIR RELATION TO THE SKIN

In many disturbances of the endocrine glands, concerning which so much has been written in the past few years, there is often an obscure interrelationship of more than one gland in the so-called "pluriglandular syndrome." The exact pathologic basis of many of these diseases is still unknown, although in some instances typical syndromes have been recognized for centuries. The skin and its accessory structures often partake of the general systemic disturbances, and not infrequently the first signs of the underlying disorder become apparent on examination of the skin.

**Myxedema.**—In this condition there is dryness and scaling of the skin with puffiness of the entire surface of the body which becomes noticeable first of all about the loose skin of the eyelids and face. Secretion of fat and sweat is diminished, the hair becomes coarse and is often lost, and an urticarial eruption may appear. There is a tendency sometimes for excessive amounts of fat to be deposited. Microscopic examination of the skin in cases of myxedema, and in states in which the basal metabolic rate is low but in which no obvious myxedema exists, reveals a chemical change in the subcutaneous tissue which suggests an excessive deposit of mucin. A form of localized myxedema has been described which is characterized by the appearance of nonpitting, edematous, tawny plaques on the lower extremities in association with paradoxical symptoms of acute hyperthyroidism of moderately severe degree. Microscopic examination of this tissue likewise reveals excessive deposits of mucin.

**Hyperthyroidism.**—In cases of exophthalmic goiter, probably particularly because of the excessive heat and moisture,

the skin is soft and thin and dermatographism and urticaria are common. Vitiligo appears more often as a disturbance of pigmentation than does chloasma. The nails may be brittle and the hair becomes sparse. It has been stated that scleroderma is commonly associated with the hyperthyroid state, but this finding does not agree with experience at the Clinic.

### **Disturbances of the Pituitary and Suprarenal Glands.**

—Cushing's syndrome is associated with adenoma of the basophilic cells of the anterior lobe of the pituitary gland, but the clinical features may also appear in association with tumors of the suprarenal cortex, wherein there is no disturbance of the pituitary gland. The disorder almost entirely affects women, and it is characterized first of all by a sudden plethoric obesity in which the fat is deposited on the face, neck, and trunk (especially prominent being the buffalo hump on the upper part of the back), and sparing the extremities. Another of the cardinal symptoms is hirsutism and, in women, this assumes the masculine characteristics. Other phases of the disorder, such as amenorrhea, hypertension and osteoporosis, do not have anything to do with the skin. In those cases in which this syndrome has been seen in association with tumors of the suprarenal cortex, the frequent occurrence of marked oiliness of the skin with acne in the usual sites has been noted, the condition affecting adults who have not previously suffered from acne. The several features of this disorder, namely, the rapidly acquired, peculiarly distributed obesity and hirsutism and the suddenly appearing acne, make one suspicious on inspection of the skin alone of a disturbance associated with the suprarenal cortex or pituitary gland.

Addison's disease, which is also directly referable to a disturbance of the suprarenal glands, has been discussed previously.

**Disturbances of the Pancreas.**—The affections of the skin which occur in association with diabetes mellitus are three: furunculosis, pruritus, and xanthomatosis, and the first two of these are probably directly attributable to the increase in the concentration of sugar in the skin. The appearance of xanthomas in diabetes will be discussed later.

**Disturbances of the Gonads.**—The evidence presented to demonstrate a relationship between disorders of the skin and

disturbances of the gonads is based largely on fancy and conjecture. However, it is quite apparent from casual observation that there is a difference in the texture of the skin of men and women, at the time of puberty, for example, the beard of the male becoming evident. In young women with acne vulgaris there is frequently a pronounced flare of the condition at the time of the menses, and in women in the third decade of life who are frail, asthenic and dysmenorrheic, an intractable type of acne of the chin often develops without the presence of comedones, and affecting this same type of young woman there has been described a rare form of dermatitis which is thought to be associated with dysmenorrhea. During pregnancy one occasionally sees a bullous dermatosis similar to pemphigus or dermatitis herpetiformis, which is known as impetigo herpetiformis. In pregnancy some common skin diseases such as psoriasis may disappear completely, only to reappear in exaggerated form within a short time after parturition. At the climacteric, in association with the disagreeable paresthesias and hot flashes there may appear troublesome pruritus of the vulva, and objective examination is frequently negative except for urticarial edema with neurodermite. This condition most frequently affects women who have had a background of urticaria and migraine, and sometimes eczema of the palms and soles. Skin tests in these cases to demonstrate an element of specific hypersensitivity are fruitless.

**Calcinosis.**—Deposits of calcium appear in the skin as localized plaques or as a part of a systemic process, but their relationship to a disorder of the parathyroid glands is not established.

**Xanthoma.**—This disease develops as a result of disturbed lipid metabolism. It is characterized by the appearance of yellow or chamois-colored papules or nodules which coalesce in masses of varying sizes and which are distributed particularly over the bony prominences of the extremities, and later, on the trunk and face and even on the mucous membranes. Examination of the blood in the more extensive forms of the disease often reveals lipemia, the lipids in the blood sometimes reaching the astounding level of 4,000 to 5,000 mg. per 100 c.c. and the blood serum to the naked eye being a milky liquid. Diabetes mellitus may be present, and occasionally there is

some evidence in the form of dwarfism or acromegaly which suggests an associated disturbance of the pituitary gland. Microscopically the individual lesions are seen to be collections of cells of characteristic structure. These cells are found at first in the neighborhood of the blood vessels and occur as the result of infiltration following resorption of the doubly refractile lipid compounds—cholesterin and the fatty acids. Both the endothelial and connective tissue cells are able to absorb these compounds. Sometimes the entire surface of the skin is tinted a chamois, pale yellow. When a strict dietary regimen is instituted, which consists of limitation of the amount of lipids, and if the diabetes which may be present is brought under control, there often results a surprising involution of the xanthomatous lesions of the skin.

**Amyloid.**—Localized deposits of amyloid may occur in the skin in the form of lichenified plaques on the lower extremities, chiefly of males who show no other disturbance of general disease. "Systematized amyloidosis," on the other hand, is the term which is applied to a rare and fatal disease wherein there is diffuse and nodular involvement of the entire skin, subcutaneous tissue, muscles, tongue, gastro-intestinal submucosa, and the walls of the larger blood vessels of the body. The spleen, kidneys and liver are spared. There is Bence-Jones proteinuria but no definite evidence of multiple myeloma. There are none of the usual causes for amyloidosis in the form of long-standing suppurations, malaria, tuberculosis or syphilis. The condition may first be recognized by the appearance of yellowish papules and nodules about the skin of the eyelids, face, neck and oral mucosa, by the waxy coloration of the skin as a whole, and by the enlargement of the tongue. Amyloid is stained selectively by Congo red dye to a pinkish red, and this affinity may be used as the basis of a test by subcutaneous injection "in vivo" of a 1 per cent solution of the dye in the vicinity of the suspected deposits of amyloid.

**Photosensitization.**—There are certain rare affections of the skin, congenital or acquired, in which there is a hypersensitivity to light of various wave lengths, particularly that in the range of ultraviolet rays. This condition may affect adults who are otherwise normal but who, when exposed to the sun, manifest pronounced urticarial or eczematous reactions; in

children, the condition frequently appears as *hydra vaccini-forme* and is characterized by marked flares in the springtime on first exposure to bright sunlight, although in more advanced cases the trouble may be apparent the year round. In both these conditions there is probably a disturbance of metabolism, as a result of which porphyrin appears in the urine and feces in abnormal amounts. The site of origin and manner of formation of porphyrin is not known definitely, but it is probable that it is an intermediate product between hemoglobin and bile pigment. Hematoporphyrin is a fluorescent substance which occurs in all normal individuals, but under normal conditions it is completely decomposed without producing untoward symptoms.

Xeroderma pigmentosum is a decidedly familial disease which is characterized by hypersensitivity to light, spotted pigmentation of the exposed surfaces of the skin, and presenile aging, with a marked tendency to the development of basal cell epitheliomas. Consanguinity may possibly be a factor in the precipitation of this disorder. In the more advanced cases of xeroderma pigmentosum the affected individuals must be protected at all times from exposure to the direct rays of the sun, either by application of protective creams which filter out specific rays of light, by covering the skin with impermeable clothing, or even by shunning light absolutely.

In certain other conditions of the skin there is a pronounced photosensitivity, namely, in lupus erythematosus, in its more acute forms, and in pellagra. Lupus erythematosus may be decidedly aggravated by exposure to natural or to artificial sunlight, and a patient in the chronic or subacute phase may sometimes suffer wide dissemination of the condition as the result of such exposure. In pellagra, the cutaneous evidences appear together with, or apart from, the other features of the syndrome, that is, the gastro-intestinal symptoms and the more or less dementia. The distribution of the eruption over the face, neck and exposed surfaces of the hands and forearms, and the pronounced recurrence in old cases during the spring and summer months, leave little doubt as to the photosensitivity that exists. It is necessary to protect the skin of pellagrins from direct exposure to sunlight for a considerable period even though the general health has been brought to somewhere more near



normal by a diet that is adequate in all respects, particularly as regards the vitamins, especially vitamin B<sub>2</sub>, which is found so abundantly in yeast.

### INFECTIONS

In no other systemic disease does the skin reflect such a large variety of indications of underlying disturbance as in the field of infections. Wile recently summarized this relationship in a discussion of what is known and what is yet unknown about focal infections. Diseases of this type which are definitely related to a primary focus are listed as follows: syphilis, tuberculosis (leprosy), trichophytosis, sporotrichosis, tularemia, blastomycosis of the systemic type, scarlatina and vaccinia. Related diseases probably are: erythema multiforme, and possibly dermatitis herpetiformis and alopecia areata. Those diseases in which the primary site is presumptive or probably in which the secondary manifestations on the skin are due to a toxin rather than to an actual dissemination of the organisms, are herpes zoster, many of the multiforme erythemas, some types of urticaria, and a few unusual "toxic" tuberculids.

In syphilis so much emphasis has been placed on the manifestations of the disease as they appear on the skin that there has been a corresponding lack of emphasis on syphilis as a systemic disease. Fortunately, with the modern methods of teaching the subject in the medical schools, with improvement of facilities for investigation of the cardiovascular and nervous systems and with the more thorough follow-up of old cases of proved syphilis, the disease has gradually outgrown the limited province of the urologist or dermatologist. The study of syphilis, of course, is a province within itself and requires first of all a thorough foundation in internal medicine. Textbook descriptions of the chancre and the secondary manifestations of syphilis are matters of common knowledge. Nevertheless it is difficult to rid the profession of the notion that all patients with syphilis must pass through these recognizable early phases. In our experience at the Clinic, in dealing with patients who are found to have latent syphilis or involvement of the cardiovascular or nervous systems, about 60 per cent of women and 40 per cent of men frankly confess ignorance of the early signs of the disease. Unrecognized, late cutaneous syphilis is be-

coming increasingly rarer with the increased threshold of suspicion for syphilis in general and the ready availability of the various specific remedies that will in most instances rapidly heal such lesions.

In a recent report on the relationship of tuberculosis to the tuberculodermas, Michelson emphasized the fact that tuberculosis of the skin is, after all, tuberculosis, and that in many instances the cutaneous signs are manifestations of an internal infection. The various types of morphologic classification serve their purpose in reflecting the grade or degree of allergy of the particular individual, but these distinctions should not divert one from the study of the relationship of the patient to the whole disease.

In the field of fungous infections it is not uncommon to see a widespread allergic reaction on the skin explained by a focal kerion; or, as has been more recently emphasized, the vesicular dyshidrotic type of eruption of the hands which follows infection of the feet with epidermophyton. In the group of focal diseases which are presumed to be due to streptococci, erythema nodosum is the outstanding example. This condition is characterized by fever and rheumatoid symptoms and by the appearance of bright red, indurated, painful nodules, usually on the lower extremities but sometimes elsewhere. The primary site of the focus is thought to be in the tonsils or teeth; but this view has not yet gained complete acceptance. Wile pointed out the difficulty of relating the cutaneous syndrome to a primary site of infection in some of the borderline conditions. This is especially true in such conditions as the exanthemas and in keratoderma blenorrhagica in which there are crusted cutaneous lesions and arthropathy in the course of systemic infection with the gonococcus.

An unusual type of extensive sloughing ulceration of the skin has been described as pyoderma gangrenosum, and it occurs in association with fever and arthritis in individuals who were debilitated as a result of some infectious process elsewhere in the body, mostly chronic ulcerative colitis. A striking parallelism was demonstrated between the degree of activity of the cutaneous lesions and the major infectious focus, and healing of the ulcers was dependent on the successful treatment of the systemic disease.

**Lymphoblastoma.**—Montgomery in a recent comprehensive summary of the cutaneous changes in the puzzling group of diseases associated with lymphoblastoma, has added emphasis to the assertion of Keim and of Wile of the striking interrelationship from a clinical and pathologic standpoint between leukemia, lymphosarcoma, Hodgkin's disease, and even granuloma fungoides. It is not my purpose here to discuss the points of controversy that arise in connection with these interrelationships. In our experience at the Clinic, taking the lymphoblastomas as a group there are cutaneous signs or symptoms of one form or another in probably a third of the cases, and in many instances these are the primary symptoms of the disease.

Granuloma fungoides is essentially a chronic disorder, although it may appear in a fulminating *d'emblée* type. It is characterized by the appearance on the skin of nodules or tumors of varying sizes which in some instances change naturally or under the influence of treatment over a period of many years. Pruritus is usually intense. In some cases before the nodules and tumors become evident there is widespread scaling of the skin with pruritus which cannot be distinguished from parapsoriasis en plaque. The histologic changes consist chiefly of infiltration of the cutis in which there is a multiplicity of cellular types together with pyknosis and karyorrhexis of the individual cells and the tendency to clumping of the endothelial or reticulum cells to form pseudo-giant cells.

In Hodgkin's disease one may recognize specific and non-specific lesions on the skin. There may be nodules with the typical architecture of the pathologic condition seen in the lymph nodes, or the skin may show a nonspecific infiltrate which is the result of an inflammatory reaction following excoriations from scratching incidental to pruritus. There may be widespread urticarial lesions, and later, a superficial scaling with the development of generalized erythroderma. In this event the microscopic picture of the skin is only rarely that of true Hodgkin's disease and the diagnosis must be made on the basis of the general examination of the patient in regard to enlarged lymph nodes, fever, and so forth, or on the basis of biopsy of one of the lymph nodes. Changes in the skin occur with sufficient regularity in Hodgkin's disease to warrant suspicion of this diagnosis whenever there is an unexplained pruritus in

association with enlargement of the lymph nodes. Sometimes there is a pronounced amount of pigmentation of unusual distribution, which has been mentioned before. Herpes zoster, and an unusual herpes simplex of severe degree, may be seen as incidental features of the disease or as the result of direct infiltration of nerve ganglions.

Of the leukemias, the myelogenous type is rare. In this connection there may be tumors of varying size on the skin or disruptions of the vascular network manifested by hemorrhages and purpura. In lymphatic leukemia the skin is frequently infiltrated with masses of the typical round cells and biopsy is quite distinctive. Circumscribed plaques or diffuse scaling erythroderma may be present. One peculiar case comes to mind of a woman whose diffuse solid edema was limited to the face and neck; this was the chief symptom of the disorder. Examination of the blood smears and biopsy of the skin revealed typical evidence of lymphatic leukemia, and there was prompt, although temporary, response to treatment by roentgen irradiation. We have seen at the Clinic, and there have been recorded in the literature, numerous examples of transitions from one phase of these conditions to another; that is, at one time the blood picture will be that of leukemia, the section of a lymph node may reveal Hodgkin's disease, and there may be fatal termination with postmortem findings of lymphosarcoma.

In lymphosarcoma there may be nodules on the skin as well as enlargement of the lymph nodes. In some cases purpura, ecchymosis and blebs appear, and in others, extensive ulcerations. In lymphosarcoma as well as in true leukemia the symptom of pruritus is less common than in granuloma fungoides and Hodgkin's disease.

It is helpful, until more is known in regard to the etiology and interrelationship of this obscure group of conditions, to maintain them as distinct entities and to record particularly those instances wherein an interrelationship is manifested. The lymphoblastomas represent one of the most unusual types of systemic disease in which the cutaneous signs are frequently pathognomonic and even may be primary manifestations of a lymphoblastoma.

## LATENT SYPHILIS AND ITS TREATMENT

PAUL A. O'LEARY

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"LATENT SYPHILIS" is a term which has steadily gained in popularity since the old idea that syphilis manifested itself in three stages only has been found to be no longer tenable. There are many reasons why subdivision of the course of syphilis into the acute, latent, and late phases has a more significant meaning than the former classification of first, second, and third stages. The latter nomenclature recognized only the acute and the late periods of the disease and completely ignored that phase which is now called "latency."

It is now readily accepted that many patients pass through the acute phase of syphilis quickly, sometimes with lesions of the skin and mucous membranes which are quite insignificant. That these manifestations of the early form of the infection are sometimes so mild as to attract no attention on the part of the patient is evidenced by the occasional case which will pass unnoticed through the hands of several medical examiners until the flocculation test is found to be positive. These cases are seen often enough in a dermatologic clinic to emphasize the point that the patient who has manifestations of late syphilis and denies a knowledge of ever having had the acute manifestations may not be falsifying; it may have been that the acute signs of the disease were so transient that they passed unnoticed.

It is likewise now recognized that all patients who acquire syphilis do not have a chancre or the clinically recognizable lesions of the skin or mucous membranes that were formerly called "secondaries." The disease in these cases quickly passes into the period of latency and only a positive flocculation test gives evidence of the infection; or the patients may be unfortunate enough to show rapid development of one or more of the late sequelæ of the disease.

Latency may be defined as that phase of the disease when neither clinical signs nor symptoms of syphilis are present. It may also be thought of as concealed or dormant syphilis. Latent syphilis has been subdivided into the early and late types, those whose latent syphilis is recognized during the first four years of the disease being in the period of early latency, and those whose latent syphilis is recognized after the disease has been present for four years or more being in the period of late latency. The significance of this subdivision will be elaborated on later in this paper. Latent syphilis presents numerous features which make it an important phase of the disease. These various factors will now be discussed in detail:

Latent syphilis is probably next to early syphilis the most frequently encountered form of syphilis. Many patients pass into the latent stage and remain there the remainder of their lives, to die of some intercurrent disease or of old age. Others pass into the latent stage, remain in it for periods of ten years or more and then manifest mild or severe clinical signs of syphilis. A much smaller group of patients never remain in the stage of latency but pass quickly through it, the clinical signs of malignant syphilis developing either in the skin, or viscera, or central nervous system within a year or so after the disease is acquired. Accordingly, it is obvious that latent syphilis is not to be considered as always being a permanent or stationary form of the disease. If, however, the type of latency develops which does remain permanent for the rest of the patient's life, he is most fortunate: in fact, syphilotherapists often strive to produce this type of latency.

Latent syphilis also has been divided into clinical, serologic, and pathologic latency by Moore and his co-workers, and it will be considered briefly under these headings.

Clinical latency exists when no clinical signs or symptoms of syphilis are discernible. This does not imply, however, that syphilitic invasion of the viscera has not occurred, because when the aorta or liver is only slightly involved, signs and symptoms are absent. These manifestations of syphilis may remain slight and the patient may be asymptomatic for years. Accordingly, the line of distinction between clinical latency and asymptomatic visceral syphilis may not be well marked and this at times constitutes a difficult diagnostic problem. Clinically.

latent syphilis may follow one of two courses: it may remain as such for the rest of the patient's life, during which he will remain free of symptoms and signs of syphilis; on the other hand, visceral syphilis may become recognizable after several years of such latency. The important point to bear in mind in regard to the management of syphilis which is latent clinically is that in some of the cases extensive treatment is warranted whereas, in others, only observation and frequent reëxaminations are indicated. In the consideration of the treatment of latent syphilis this point will be discussed in more detail.

Serologic latency implies that, although serologic tests are negative, the patient still has active foci of syphilis. Ten years ago, when the serologic technics were less sensitive than they are at present, serologic latency was very common; however, with the advent of the newer flocculation tests, serologic latency was encountered less frequently, and with the advent of still more sensitive serologic technics which no doubt will be developed in the future, serologic latency will be even less common than it is now.

Pathologic latency means that active *Spirochæta pallida* are present in the tissues, but that a pathologic reaction on the part of the host to the invader, in the form of a minute or massive gumma, is lacking. This conception of latency was advanced by Warthin, who demonstrated *Spirochæta pallida* in the cardiac muscle and testes of patients with latent syphilis in the presence of mild pathologic changes. For many years this was the basis for the conception that latency was characterized by the development of nests of *Spirochæta pallida* which might remain dormant for years or might at any time become active and produce clinically recognizable manifestations of syphilis. The proof that the state of pathologic latency exists is dependent on the findings at necropsy, and this is a pathologic problem which is still subject to debate.

A diagnosis of latent syphilis is made possible by recognition of the status of the patient as conforming to the following criteria:

1. If a history of acute syphilis is elicited, the disease may be classified as early latency if it is of less than four years' duration, or as late latency if it is of longer duration.
2. The clinical examination must be negative for signs of

syphilis. This of necessity includes examination of the skin, mucous membranes, special senses, central nervous system, and the bony structure. If manifestations of the disease are found on such examination, the patient is no longer considered to have latent syphilis.

3. Examination of all the factors in the spinal fluid must be negative.

4. An examination of the cardiovascular system must be negative in that no signs of aortic stiffening or enlargement, aortitis, aortic valvular incompetency, or aneurysm must be noted. This examination should also include teleroentgenographic examination of the thorax.

5. The flocculation, precipitation, or complement-fixation reactions of the blood may be either negative or positive.

6. When the foregoing factors are once estimated, repeated reexaminations at annual intervals are necessary to determine that their status remains unchanged and that clinical signs of syphilis do not become manifest. Accordingly, a diagnosis of latency is not possible at the first examination but can be made only after the clinical and laboratory status has been determined and repeated examinations at subsequent periods of observation have indicated that the latent phase is of a permanent nature. Each annual reexamination that reveals no change in the patient's status adds material significance to the value of the diagnosis, and each year thereafter that the examination shows no change indicates that the latency is becoming more permanent.

Latency has another important factor, namely, that of resistance or the defensive mechanism. It has already been pointed out that latent syphilis is divided into early and late latency. This subdivision is made because it is during the first four years of the disease that the patient's defensive mechanism against the infection shows signs of developing. This fact is well illustrated in a study of the spinal fluids of patients during the first four years of their disease. Briefly this study revealed that in a group of patients who had received no treatment for syphilis and who had had the disease for a year or less, examination of the spinal fluid revealed abnormalities in 33 per cent of the cases; during the second and third years the incidence of positive spinal fluids was respectively lower, and



by the fourth year the incidence of spinal fluid abnormalities had decreased to slightly more than 1 per cent.

It has likewise been shown that if a positive spinal fluid has not developed by the fourth year of the disease, the chances are 99 per cent in the patient's favor that his spinal fluid will henceforth remain negative. No doubt a similar situation prevails in regard to cardiovascular involvement, but at this time there is no way by which the earliest involvement of the aorta can be determined. The factor of resistance is essential to the development and maintenance of latency, but there unfortunately is no rapid method by which one can appraise a patient's resistance to syphilis. A means of measuring the defensive mechanism of the patient against the disease is one of the paramount problems which today confront the syphilologist. The development of nonspecific therapy has been the result of an effort to stimulate these factors of resistance against disease. It may be said, however, that a patient who manifests and maintains latency has organized or is in the process of organizing a satisfactory defense against the infection.

It is unfortunate that all patients for whom a tentative diagnosis of latent syphilis is made do not remain in that state. The time factor and the acumen of the diagnostician are factors which materially influence the frequency with which such progression of the disease is noted. When the diagnosis of latent syphilis is made in a case in which the disease is of fifteen or more years' duration, the state of latency will probably remain permanently. On the other hand, a similar diagnosis made when syphilis is of approximately five years' duration usually means that treatment and more frequent annual examinations are necessary to make certain that latency is maintained. The reason for this is that the great majority of the serious sequelæ of the disease are recognizable by the fifteenth year.

When signs of cardiovascular syphilis develop while a patient is under observation for latent syphilis, the diagnosis of latency is immediately discarded. On the other hand, if a patient with clinical signs of neurosyphilis becomes serologically negative and free from symptoms, the diagnosis remains neurosyphilis but may be qualified by the addition of the term "arrested": in such a case a diagnosis of latency is not possible.

In the essentials laid down for the making of the diagnosis

of latency the comment was made that the serologic tests of the blood may be negative or positive. This is simply another way of saying that latent syphilis may be recognized and so diagnosed irrespective of the blood tests. If a patient is adequately treated for acute syphilis and a negative flocculation or Wassermann test develops and he has a negative spinal fluid and examination of the cardiovascular system is negative, a diagnosis of latent syphilis is warranted. Repeated reexaminations which show an unchanged status for a five-year period may then permit of "parole" or even of the diagnosis of "cure." If a similar patient with early syphilis is likewise adequately treated but retains the positive flocculation or Wassermann test, although all other examinations are negative the diagnosis of latency is also permissible even though there may be need for further treatment; the likelihood of clinical progression, however, must be constantly borne in mind. If the patient with latent syphilis has had the infection for many years and the serologic tests spontaneously change from positive to negative, the diagnosis need not be changed. It is quite common to encounter a patient who has had syphilis for many years and whose serologic tests remain positive. These cases cause both the physician and patient considerable concern because of the inability to obtain a negative blood test.

Thus far I have endeavored to show that the status of the serologic test of the blood is of no significance in latency, although it must be emphasized that the diagnosis of latency is warranted only after examinations of the spinal fluid, cardiovascular and visceral systems and special senses are negative. It is unfortunate that latent syphilis and Wassermann-fastness are frequently confused. Latency may accompany Wassermann-fastness. However, Wassermann-fastness is frequently the result of aortic disease or a positive spinal fluid. Accordingly, when the question is asked as to how to treat a Wassermann-fast patient, the answer must be to determine first, if possible, why the blood test remains positive, such investigation to include the same diagnostic procedure used for the recognition of latency. As Wassermann-fastness may be due to syphilitic visceral disease and may be a part of latency, the patient who has a permanently positive blood test must be scrutinized more frequently for signs of clinical progression of the disease than the serologically negative patient with latent syphilis.

The treatment of latent syphilis is the treatment of the problem presented by the individual patient, because it is not logical to systematize treatment of this phase of the disease in a manner similar to that in which treatment of acute syphilis can be regimented. It is possible, however, to discuss to a certain extent the systematic treatment of latency when the cases are grouped according to the duration of the syphilis, the age of the patient and the amount of previous treatment. It should be recognized, however, that these suggestions in regard to the treatment of latency are flexible and that numerous factors, such as the patient's personality, the degree of syphilophobia present, and the status of his health aside from syphilis, are of great weight in deciding that treatment is or is not necessary. The discussion of treatment lends itself to the citing of various case types which illustrate the variables in the treatment of latent syphilis.

In the case of the young adult whose syphilis is of five years' duration and is in the latent phase and whose serologic test of the blood is positive, the amount of treatment previously received and the patient's sex are of importance in determining the therapeutic program. If the patient is a young man of thirty-two or thereabouts who has had long and intensive treatment with a minimum of fifty injections of arsphenamine and twice as many injections of bismuth or mercury, it will probably be advisable to place him on observation and have him undergo annual reëxaminations. If it seems feasible he may, however, be given two courses of bismuth, fifteen injections each, twice a year for three years, following which observation periods may be instituted. If a patient of similar age whose syphilis is also of five years' duration had received a comparatively small amount of treatment at the time he had acute syphilis, that is, eight to ten injections of arsphenamine and fifteen to twenty injections of bismuth, it would seem advisable to give him a complete course of treatment, consisting of at least thirty injections of an arsphenamine and sixty injections of one of the heavy metals, followed by two or three years of bismuth therapy as outlined in the previous instance.

The sex factor adds a somewhat different aspect, inasmuch as in women of this age the likelihood of pregnancy requires that in the presence of latency and positive serologic tests the

treatment be more strenuous and prolonged. Especially is this true if the patient becomes pregnant, because latency does not assure the mother of a nonsyphilitic offspring. Prolonged and repeated courses of bismuth have been more successful in producing serologic negativity in cases of latent syphilis than have combined arsphenamine and bismuth therapy, and they have proved decidedly superior to treatment by arsphenamine alone.

In the case of middle-aged adults the sex of the patient is of less significance because there is less likelihood of pregnancy. The male adult of forty-five who acquired the infection fifteen years previously and is found to have latent syphilis and a positive blood test presents a problem in which the need for treatment is materially influenced by such factors as his general health, his attitude toward his condition, and the amount of previous treatment. If treatment was wholly inadequate at the time the acute signs of the disease were present, or if the presence of the disease was unknown prior to the time of examination and no previous treatment had been received, it is probably advisable to give several courses of arsphenamine and bismuth or mercury, followed by several courses of bismuth each year for two years. However, if the patient has received a great deal of treatment off and on for many years but the serologic tests have been uninfluenced by it, it is advisable to place him on observation. He should be reexamined annually to make certain that the positive test is not due to syphilitic aortic disease or to some other visceral complication. If a spinal fluid test was found to be negative during latent syphilis, repetition of the test is not necessary. Reassurance that the positive blood test is not attributable to visceral syphilis or to syphilis of the central nervous system is a means of educating these patients to the insignificance of the positive blood test. The experience of those who have used nonspecific therapy in a large group of cases of latent syphilis in which a control study was carried on simultaneously on a similar series of patients who were only observed and were not treated, shows that nonspecific measures in the form of fever therapy of all sorts are of no material value in reversing the serologic test to negative. In a group of patients with latent syphilis, observed for ten years, who did not receive treatment of any type, 85 per cent became serologically negative and showed no signs of clinical progression.

A third group of patients includes those with latent syphilis who are approximately sixty years of age and who have had syphilis for thirty years or longer. The factors of sex, previous treatment, and the patients' concern over the presence of the disease are of less significance than in the cases previously cited. In the majority of these cases the presence of the disease may well be ignored; occasionally, mercury and chalk and small doses of potassium iodide may be given by mouth; only rarely is it necessary to give such patients arsphenamine and bismuth. These patients have controlled their infection satisfactorily for thirty years, they are asymptomatic and free from signs of syphilis, and have long since passed the time when the great bulk of patients with syphilis manifest the serious complications of the disease. Accordingly, such patients are not in need of drastic treatment because of a positive Wassermann test but only of treatment for syphilis as it influences some other intercurrent disease.

In between these three main groups of patients there are many different manifestations of latent syphilis, and in some instances treatment is advisable and in others is unnecessary. In determining the need for treatment of these patients, the potency of the associated findings, the significance of the historical data, and the willingness of the patient to coöperate by reporting for annual reëxaminations are the factors which are to be considered in conjunction with the thoroughness of the examination which warranted the diagnosis of latency.

Latent syphilis, especially during the late phase, is for all practical purposes not considered as an infectious period of syphilis. Treatment is rarely needed to prevent dissemination of the disease to others by patients in this stage.

#### SUMMARY

Latent syphilis is a transient or permanent phase in the course of syphilis. It can be diagnosed as such only after a thorough series of examinations and tests which eliminate the presence of active syphilis. Observation of the patient over a period of years may be necessary to substantiate the diagnosis. The flocculation or complement-fixation test may be either negative or positive in latent syphilis. The need for treatment

of a patient with latent syphilis is dependent on the age of the individual and the duration of his disease. These data may be augmented by the amount of previous treatment, the thoroughness with which the examinations were carried out in the making of the diagnosis, the status of the patient's general health otherwise, the possibility of pregnancy, and the patient's attitude toward his disease.

## FEVER THERAPY FOR GONOCOCCIC INFECTION: III

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MARCH, 1935, we reported the results obtained with fever therapy in thirty-three cases of gonococcic infection of the urethra, epididymis, prostate gland, uterus, fallopian tubes, and articulations. Of the twenty-nine cases in which the patients had received complete treatment before that date, in twenty-five (86.2 per cent) complete and permanent cure resulted. The average number of sessions of fever required to effect a cure in the majority of cases was found to be 5.4. For a time, before March, 1935, the patients were uniformly subjected to five hours of sustained fever, with the rectal temperature between 106° and 107° F. (41.2° and 41.7° C.), and this was repeated from three to eight or even ten times at intervals of from four to seven days. It was soon discovered that, with such relatively long intervals between sessions, the urethral or vaginal discharge returned. At that time, in fact, the return of urethral or vaginal discharge was empirically regarded as a sign that further treatment was necessary. It was apparent that the intervals between sessions of treatment were too long, and the first improvement in technic was to shorten this interval, because it was realized that to wait for the return of discharge was undoubtedly to lose some, if not most, of the advantage gained. Thenceforth, an interval of two days between sessions was allowed, and the results improved considerably. In spite of this improvement, however, the condition in an appreciable percentage of cases proved resistant to treatment. As previous experience had led to the conviction that the two principal factors in the influence of fever on gonococcic infection were the degree and duration of the temperature, the next step

seemed to be to increase the length of the sessions. However, since various reasons, such as the sensitiveness of the skin of some patients or the importance of allowing the cardiovascular system to adapt itself to the treatment, made it seem unwise to increase the duration of the initial sessions, these were not prolonged beyond five or six hours at temperatures of 106° to 107° F. But if, after the second session, the smears and cultures were still positive, the third session was extended to eight hours. After one or two sessions of eight hours at the same temperature, if the smears and cultures still remained positive, the next session was extended to ten hours. Fortunately, it was found that in only a minority of cases were more than five sessions required. Nevertheless, in a few cases, even after several sessions of from five to ten hours, gonococci could still be found. When the patient was able and willing to continue, sessions of twelve hours at the same temperature were given, and the infection was cured. In a few other cases in which the condition forbade such prolonged treatments, or the patients were unwilling to submit to them, the infection was not cured. The reason for such failure in a small percentage of cases undoubtedly was that the strains of gonococcus responsible for the infection in these cases were exceptionally resistant to heat.

As a result of the foregoing improvements in technic, the percentage of cases in which cure was effected increased to 92, as reported in 1936. Since then the treatment of acute and chronic gonorrheal urethritis, with or without complications, has continued along much the same lines and with only slight additional modifications in technic.

Our present purpose is to report the results obtained from the inception of this work to July 1, 1936. From the very beginning, by the way, the cases selected for treatment have been chosen by the clinician and the urologist, and the question of cure has been decided by the urologist and clinician, after repeated negative smears and cultures. At no time have the physicians who supervised the treatment had any voice in deciding whether any patient was or was not cured.

Another point must be made clear. This is that when repeated smears and cultures have shown that a patient was apparently cured, we have nevertheless insisted in every case on



giving two additional sessions of treatment, in order to prevent any possibility of recurrence. That this policy has been wise is shown by the fact that, whenever a patient returned three or more weeks later and tried to make us believe that he was the victim of a recurrence, we have always succeeded in making the patient admit another exposure.

We are aware that the technic employed has been criticized by some observers on the grounds that a cure requires too many sessions of treatment, and that such an "excessive number of sessions is unnecessary." Those who have made this criticism have not taken into consideration the circumstances under which the work is done, and have not realized that this deliberate policy is dictated by sound reasons. Most of the patients referred to us for treatment come from distances varying between 50 to 1,800 miles, and they come in the expectation of being completely cured. Therefore, it has seemed to us essential to arrange the scheme of treatment so that an absolute cure could be assured to the largest possible number of patients, regardless of other considerations. Moreover, the high percentage of cases in which a complete and permanent cure has been obtained seems fully to justify the technic adopted. When others can show equal or superior results, with a technic that involves fewer sessions of treatment, further technical modifications will be considered, but not until then.

Between December 1, 1933 and July 1, 1936, 210 patients suffering from acute or chronic, simple or complicated, gonorrheal infection were referred for fever therapy. Of this number, forty-one patients did not complete their treatment or the idea of treating them had to be abandoned for various reasons. Sometimes this was because the patient lacked stamina; sometimes it was because of peculiar reactions of the cardiovascular system which made it unwise to proceed further, but in most cases it was because after the initial session, the patient failed to return for subsequent sessions. In any event, these cases must be excluded from consideration. Of the 169 patients who took the treatment faithfully, 152 (90 per cent) were cured and have not had any further physical difficulties caused by the gonococcus. Seventeen patients (10 per cent) were not completely cured, but their condition improved to varying degrees. Among the 169 patients who completed the course were 112

(66.2 per cent) males and fifty-seven (33.8 per cent) females. Ninety-seven (57.4 per cent) were single, and seventy-two (42.6 per cent) were married. The average duration of the infection had been three and three-tenths months. One hundred nine (64.4 per cent) patients had contracted the infection for the first time, whereas sixty (35.6 per cent) had contracted it for the second or third time.

Of the 152 patients who were treated successfully, only thirty-one had simple gonorrheal urethritis. In 121 (79.6 per cent) the infection was associated with various complications. Thirty-six patients had prostatitis; thirty-five had gonococcic arthritis; twenty-six had infection of the pelvic structures; two had infection of Bartholin's glands; seven had epididymitis; four had a urethral sinus; one had fibrositis; of one the seminal vesicles were involved; two patients had proctitis; two had cystitis, in one case the ureter was infected; one patient had pyelitis; two had an abscess of the prostate gland, and one had periurethral inflammation.

In nineteen cases smears and cultures were negative and remained negative after a single session of treatment. In forty-eight cases smears and cultures were negative and remained negative after two sessions of treatment. In thirty-seven cases smears and cultures were negative and remained negative after three sessions of treatment. In twenty-three cases smears and cultures were negative and remained negative after four sessions of treatment. In nine cases smears and cultures were negative and remained negative after five sessions of treatment. In seven cases smears and cultures were negative and remained negative after six sessions of treatment. In one case smears and cultures were negative and remained negative after seven sessions of treatment. In five cases smears and cultures were negative and remained negative after eight sessions of treatment. In two cases smears and cultures were negative and remained negative after nine sessions of treatment. In one case smears and cultures were negative and remained negative after ten sessions of treatment.

Thus it will be seen that in 127 of 152 cases (83.5 per cent), from one to four sessions of treatment were sufficient to rid the patient of the infection. In 136 cases (89.5 per cent), from one to five sessions of treatment were sufficient. In only six-

teen cases (10.5 per cent) were more than five sessions of treatment required to eradicate the gonococcus.

It may be interesting to mention the character and frequency of occurrence of certain disturbances observed during the course of the treatment, and either directly or indirectly caused by it. At some stage of treatment, varying degrees of nausea and vomiting were observed in fifty-seven cases. Sometimes this occurred at the beginning of a session of treatment, when the patient had disregarded the physician's warning not to eat before reporting for treatment. Usually, however, this complication developed at the end of a session or soon after its completion. Having reason to think that this tendency of certain patients might be related to the drinking of 0.6 per cent saline solution while in a fasting state, we attempted to overcome it in two ways: by diminishing the salt content of the solution to 0.3 per cent, and by giving to some patients, from time to time, a small quantity of milk. This last step was intended to quiet the hunger pain so distressing to certain patients, because it was felt that the pain might, in part at least, be the cause of the nausea. That this has been a factor seems established by the fact that a smaller percentage of the patients who were given milk to drink during treatment were disturbed by nausea. However, this has not been tested for a sufficiently long period to warrant absolute conclusions. The percentage of salt in the solution was diminished because it was thought that in some cases the vomiting was probably caused by overfilling the stomach with salt solution. Of course, it was realized that an excessive quantity of water, aside from its salt content, might be responsible for the disturbance, but this seemed a less likely cause than an excess of salt. This technical modification also will have to be tested for a much longer time before the relationship between the percentage of salt and the nausea and vomiting can be ascertained.

Headache is a frequent complaint of patients who receive fever therapy for any disease. It is especially common among patients, the effective treatment of whose condition requires that a high temperature should be maintained for several hours. Eighty-six (56.6 per cent) of the 152 patients included in this report complained of headache. But since, in almost all cases, the headache disappears spontaneously in from one to three

hours after the completion of a session of treatment, special measures to combat this symptom are seldom necessary.

Small, cutaneous vesicles were observed in thirty-eight cases. They promptly responded to ordinary measures and did not have any particular significance. Most certainly they do not justify apprehension, and should not be allowed to interfere with treatment.

Herpes of the lips and sometimes of the nose occurred in thirteen cases. This complication usually developed after the first session of treatment, in patients who admitted being prone to herpes. The lesions should be treated on general principles; they heal rapidly, and seldom need they interfere with the orderly sequence of the sessions of fever.

Tetany, usually affecting the hands and feet, was observed in five cases. In another case the tetanic manifestations did not affect the muscles of either the hands or feet, but did affect those of the abdominal wall. In some cases the intramuscular injection of 10 c.c. of calcium gluconate was sufficient to stop the disturbance. In other cases in which calcium gluconate was less effective, or ineffective, the inhalation of carbon dioxide promptly arrested the tetanic manifestations. As a result of this experience, we have come to rely on carbon dioxide rather than on calcium gluconate. In five other cases peculiar, incoordinate, muscular twitching was encountered. This resembled closely the muscular twitching of certain patients when their temperature rises above a certain level. The cause or causes of such twitching are not clear. In three cases a peculiar palsy of the peroneal nerve was observed; in two cases the palsy continued for one month, and in the third case for about five months. It then disappeared entirely. In all three cases the patients had received ten or more sessions of fever, and some of the sessions had been exceptionally long.

Among the fifty-seven patients who had nausea and vomiting, the material vomited by six contained streaks of blood. Since in not a single case could a gastro-intestinal lesion be found to account for the small quantity of blood, the streaks of blood were thought to be attributable to rupture of capillaries in the gastric or esophageal mucosa resulting from the patient's retching.

One patient had diarrhea; therefore, it does not appear likely that the intestinal disturbance was related to the fever.

#### COMMENT

To say that fever therapy is entirely devoid of danger is contrary to fact. To date, the number of patients treated for various conditions has been 516, and these patients have received approximately 2,580 sessions of treatment. Of this number, one patient died under treatment. The patient was a young woman who had a pelvic infection. She had almost completed her first session of treatment, which had been entirely uneventful, when the pulse rate suddenly fell. She was immediately withdrawn from the chamber; restoratives, including carbon dioxide and oxygen, were administered, epinephrine was injected into the heart three times, but, although the heart began to beat after each injection of epinephrine, respiration failed to return. It is not clear what may have been the factor or factors responsible for her death. This patient's temperature had risen readily, and not the slightest difficulty had been encountered in maintaining her temperature. At no time during the session had her temperature risen as high as 107° F. until just before the pulse collapsed.

This single death among the 516 patients treated gives a mortality of less than 0.2 per cent. Small though this is, the realization that death may occasionally occur from any method of treatment still offers no consolation for the loss of a patient.



## THE DIAGNOSIS AND TREATMENT OF LOW BACK DISABILITY

RALPH K. GHORMLEY

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THE ever perplexing problem of low back pain may be said to rank among the most important of those problems which confront members of the medical profession today. It produces a tremendous amount of disability and at the same time economic loss of extraordinary importance, as anyone interested in industrial medicine can well testify. That many cases of low back pain are of minor importance is well recognized. The average individual who is troubled by such a pain, if it is transient, usually is able to recover without any serious loss of time or absence from work. However, low back pain, even if minor in nature, becomes of the greatest importance to the patient who is in the least introspective. In another large group of cases severe symptoms are produced; these cases demand serious consideration and the utmost in the way of medical effort and care.

As a working basis, the causes of low back pain can be classified. There is no established classification of back disabilities and many physicians may find suitable to their needs classifications other than that which follows:

1. Posture:
  - (a) Chronic postural strain:
    1. Lumbosacral or sacro-iliac lesions.
2. Trauma:
  - (a) Trauma involving vertebra:
    1. Fracture:
      - (a) Bodies.
      - (b) Pedicles—may produce spondylolisthesis.
      - (c) Laminæ.
      - (d) Facets.
  - (b) Trauma involving joints:
    1. Traumatic spondylosis.

- (c) Trauma involving disks:
  - 1. Narrowing of disk.
  - 2. Avulsion of disk.
  - 3. Rupture of nucleus pulposus.
- 3. Infection:
  - (a) Arthritis, infectious.
  - (b) Spondylitis deformans or spondylose rhizomelique.
  - (c) Fibrositis.
  - (d) Typhoid spine.
  - (e) Tuberculosis and so forth (real localized infections).
- 4. Metabolic and senescent conditions:
  - (a) Hypertrophic changes (may be traumatic).
  - (b) Osteoporosis with pathologic fracture.
- 5. Congenital anomaly:
  - (a) Spina bifida.
  - (b) Sacralization of fifth lumbar vertebra or lumbarization of first sacral vertebra.
  - (c) Anomalous facets (may produce spondylolisthesis).
- 6. Neoplastic conditions:
  - (a) Benign tumors:
    - 1. Osteoma and osteochondroma.
    - 2. Giant cell tumor.
    - 3. Hemangioma.
  - (b) Malignant tumors:
    - 1. Metastatic from prostatic and mammary carcinoma, and so forth.
    - 2. Myeloma.
    - 3. Primary osteogenic sarcoma.
    - 4. Ewing's tumor, and so forth.
- 7. Neurologic conditions:
  - Tumors of the spinal cord and so forth.

The foregoing outline covers most of the possible causes of low back pain. To place a given case of backache in its category may at times be very difficult. More than one of the conditions named may be present in the same case and actual identification of the case with a definite cause may be out of the question. However, in order to approach the subject with the necessary facts in mind a fair understanding of all of the conditions mentioned in the outline is desirable.

The relative incidence of cases attributable to the various causes is of some importance. Chronic and acute strain accounts for a fairly large percentage of the cases and these cases predominate if those of strain caused by trauma are included. The group of cases caused by infection is a large one.



too. Infection and trauma may co-exist in any one case. Actually it is difficult to prove that an "infectious" backache is such. A focus of infection is found in such a case. The focus is removed and after its removal the patient's condition improves. Unfortunately that is about all the proof ever obtained to show that the condition was in any way attributable to a focus of infection. In many cases that is all that is necessary so far as the patient is concerned but from the standpoint of scientific analysis much is lacking. Besides in such a case treatment rarely is limited to removal of foci only and it is difficult to evaluate the relative importance of all of the measures used.

#### PATHOLOGY

The pathology of low back pain is little understood. Marked lesions, such as those of tuberculosis, of malignancy and other destructive lesions are obvious. The great majority of cases of backache, however, are out of the realm of study by a pathologist. Rarely, if ever, does a patient die of a backache. Therefore, the opportunity to describe pathologic changes that may or may not be accountable for the symptoms almost never arises. At times study of tissue removed when operation is performed may reveal changes in the lumbosacral articulations and in the sacro-iliac joints. Smith-Petersen studied the tissue removed from sacro-iliac joints and found "surface fibrosis, myxomatous degeneration of the matrix, replacement fibrosis and calcification." At the Clinic we have studied the changes in articular facets removed at operation and have found the changes typical of traumatic arthritis, that is, fibrillation, and later degeneration of the cartilage with eburnation of the underlying bone. The work of Schmorl has done most to stimulate interest in the pathologic changes in the intervertebral disks. These changes may be the most important of all in cases of chronic lumbosacral strain. Geist was one of the first to emphasize these changes. Williams pointed out the importance of changes in the disks in cases of lumbosacral pain with sciatica. Mixter and Barr reëmphasized the fact that avulsion of the disk into the spinal canal may occur and thus give rise to symptoms. They expressed the

belief that this is a much more common condition than heretofore has been recognized. Freiberg and Vinke gave the most plausible explanation of the association of sciatic pain with changes in the sacro-iliac joint.

With this brief sketch of the up-to-date concepts of the pathologic changes which underlie the more common types of low back pain, it may be admitted that there is still a great deal to be learned on the subject.

## HISTORY

Taking of the history in this condition, as in any other disease, must be accurate and careful. Indeed it may be the most important of all the procedures. Before or during the taking of the history the patient's background with reference to the pain should be learned. This is most important in industrial insurance or medicolegal cases and may be very difficult to obtain from the patient himself. In other cases, not in any way complicated by the problem of industrial compensation, the patient may have set up certain conceptions of his own such as "that the pain is due to kidney trouble" or "a vertebra is out of place" and many other misconceptions to expression of which the inquirer must listen patiently and then get his own history by direct questioning.

In taking the history certain facts must be brought out, among the most important of which are: (1) mode of origin, whether insidious or following injury; (2) type of pain, whether static or constant and whether appearing at night or in the morning; (3) means of relief of pain, whether relief can be obtained by rest, application of heat, and so forth.

If from the preliminary inquiry a true insight into the patient's status relative to industrial compensation or medicolegal involvement is not obtained, effort should be made by other means to get this necessary information. The physician must obtain it before he can deal intelligently with the case.

It is often helpful, before formulating treatment, to inquire of the patient what other treatment has been tried, if any, and with what success. In many instances if adequate conservative measures, under the direction of competent physicians, have failed, much time can be saved by not repeating those measures.

## EXAMINATION

Examination of a patient troubled with low back pain always should be carried out with the patient's back and hips well exposed. If a cape is worn, it should be reversed, exposing the entire back.

With the patient standing, the following should be sought: the presence of list or sciatic scoliosis (Fig. 42); flattening or



Fig. 42.—Typical attitude in sciatic scoliosis. The list may be toward or away from the painful side.

increase of lumbar lordosis; atrophy of buttocks; prominence of the hip and so forth.

The patient should be asked to bend forward and then the physician should note particularly whether spinal motion is limited and to what degree. The normal spine should arch in the lumbar region on bending forward. The patient should keep his feet on the floor and his knees should not be flexed as he bends forward. When he bends to the side his elbows

should be in the plane of the body. In this way the spine is straightened and the exact amount of bending to the side can be accurately noted.

Regions of tenderness should then be noted. The presence of tenderness is usually best determined by observing the patient's response to pressure. Deep pressure is often necessary, particularly if patients are obese or heavily muscled. Real pain will be elicited in many cases and will be manifested by wincing, squirming or a protest on the part of the patient. Percussion with the fist over the spinous processes using a knuckle to strike the bony prominences, may help to elicit deep-seated tenderness. Percussion should be used over the posterior superior portion of the spinal column. Any prominences, such as the trochanters and iliac crests, should be palpated to determine the presence or absence of tenderness.

Smith-Petersen has outlined a routine examination in such cases which may be of help to those interested in this subject. The same author has described in more detail his method of examination in Christopher's "Textbook of Surgery."

After examination in the standing position, the patient should be allowed to sit on an examining table with knees and hips flexed. Motions should again be observed and tender regions noted.

With the patient supine, his ability to tolerate raising of the straight leg should be tested and Gaenslen's test should be carried out. The legs should be measured. Ober's test for contracture of the iliotibial band also should be done. This test is carried out as follows: "The patient lies on his side with the thigh next to the table and flexed enough to obliterate any lumbar lordosis. The upper leg is flexed at a right angle at the knee. The examiner grasps the ankle lightly with one hand and steadies the patient's hip with the other. The upper leg is abducted widely and extended so that the thigh is in line with the body. If there is any abduction contracture the leg will remain more or less passively abducted depending upon the shortening of the iliotibial band. This band can be easily felt with the examining fingers between the crest of the ilium and the anterior aspect of the trochanter."

The patient should then be asked to lie prone on the examining table, when again regions of tenderness should be

noted and hyperextension of the hips, as well as rotation of the hips, should be noted.

With these facts in hand the physician can come to some conclusion regarding the type of lesion he is dealing with. Of the various points in the examination, consistently localized tenderness probably is of the greatest importance in determining the type of lesion. Tenderness, of course, is a subjective manifestation and therefore its importance may be questioned. In most instances an experienced examiner can tell whether a patient's response to percussion or palpation is overdone or feigned. The moment of response is never accurately timed by the malingerer. He responds too quickly as a rule; sometimes too slowly. His attitude in other ways is often characteristic of the "compensation neurotic" and gives him away.

Limitation of motion, if marked, generally indicates an inflammatory process, that is, some type of arthritis, spondylitis or myositis. Usually, motion of patients who have sacro-iliac strain is not limited when they are in the sitting position, whereas in cases of lumbosacral strain motion is limited both when the patients are standing and when they are sitting.

When examination of the back has been completed the question remains as to how much of a general examination is necessary. In the average case of acute back strain no further examination usually is necessary. In cases in which the condition has become chronic, or in any case in which infection may be suspected as the basis of the difficulty, complete examination should be carried out. This should include routine examination of heart, lungs and abdomen; search for foci, particularly about the teeth, the tonsils, the prostate gland of the male and the general pelvis of the female. If there is any sciatic pain, neurologic examination should be made. Such an examination should be done by one who is familiar with neurologic conditions if a competent neurologist is not available.

Laboratory examinations of importance are urinalysis, flocculation tests, estimation of hemoglobin and enumeration of leukocytes. Roentgenologic examination will be discussed more fully later. If neurologic examination gives sufficient evidence to warrant lumbar puncture this should be done and the spinal fluid should be examined. The total protein is the most important factor in examination of spinal fluid.

The roentgenologic examination should include, as a very minimum, anteroposterior and lateral (Fig. 43) views of the



Fig. 43.—Lateral view of lumbosacral joint.

lumbosacral regions, including the lower lumbar vertebræ, the sacrum and the sacro-iliac joints. If these last are the center



Fig. 44.—*a* and *b*, Three-quarter views in the same case as that represented in Fig. 43. In *b*, the damaged facet is clearly seen and is indicated by arrows

of attention, stereoscopic anteroposterior views should be made. or changes in these joints, unless they are extensive, cannot

be accurately read from flat plates. In addition to the foregoing views, oblique views to demonstrate the lower lumbar facets should be made (Figs. 44 and 45). Finally, if the lumbar puncture and the neurologic examination arouse suspicion of a damaged intervertebral disk or of tumor, lipiodol should be injected and roentgenologic examination made. Thus, a formi-

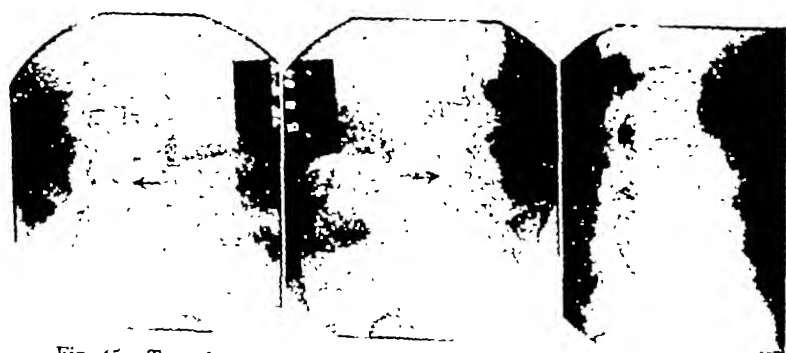


Fig. 45.—Two three-quarter views and a lateral view in a case of lumbo-sacral spine. Bilateral damage to facets is evident between fourth and fifth lumbar vertebrae.

dable array of roentgenologic examinations may be necessary before completion of the studies in one of these cases.

The important features to note in examination of roentgenograms are:

1. Sacro-iliac regions:

(a) Presence of marginal osteitis.

(b) Destructive changes:

1. Inflammatory.

2. Malignant.

(c) Irregular destruction such as is seen in early spondylitis deformans.

(d) Fusion.

(e) Hypertrophic marginal changes (often of little or no significance).

2. Lumbo-sacral joint:

(a) Changes in bone:

1. Marginal hypertrophic changes.

2. Shape and size of vertebral body.

3. Character of bone, particularly evidence of osteoporosis.

4. Congenital anomalies, particularly spina bifida and sacralization of the transverse processes. If sacralization is present, whether it is complete or whether there is an obvious joint between the process and the sacrum should be noted.

5. Destructive lesions: malignant, inflammatory.

6. Sclerosing lesions: malignant, inflammatory.
  7. Presence of spondylolisthesis.
- (b) Changes in disks:
1. Narrowing or thinning of disk.
  2. Ballooning of disk associated with osteoporosis of vertebræ.
  3. Increased density of margins of the vertebræ.
  4. Prolapsed nucleus pulposus (Schmorl bodies).

### DIFFERENTIAL DIAGNOSIS

In dealing with low back pain of all sorts, neurologic conditions must be thought of first in differential diagnosis. The outline of examination which has been given has revealed the importance of the opinion of a neurologist; in many instances this may be said to be an essential part of the routine examination.

Inflammatory lesions, such as those of tuberculosis, must be excluded. As a rule evidence of tuberculosis of the lower lumbar vertebræ or sacro-iliac joints can be fairly readily recognized in the roentgenogram. Often, too, an abscess is present either in the iliac fossa, the gluteal region, or below Poupart's ligament. Such an abscess often produces spasm of the psoas muscle on the side affected and a "soft-parts shadow" may be visible in the roentgenogram.

Other inflammatory lesions occasionally may be seen, particularly those which accompany acute or subacute infections of pyogenic origin. In the presence of such lesions there are, as a rule, signs of infection, fever, localized softening, inflammatory masses, abscesses and so forth. Occasionally a sacro-iliac joint may become fused by an acute infectious process without any suppuration.

Tumors, both benign and malignant, must be ruled out. The subject of neoplasms of bone is such an extensive one that elaborate consideration must be omitted here. However, it is well to remember that such tumors do occur and may constitute a troublesome diagnostic problem. As a rule any low back pain that does not subside under a reasonable amount of treatment of the types usually given must be suspected of having its origin in a malignant neoplasm. Sometimes such a lesion will not be found at the time of examination and it will be necessary to ask the patient to return at a later time for reëxamination.



In examination of females the various possible pelvic lesions must be ruled out by examination of the pelvis. As a rule, the skeletal types of backache are not so much exaggerated during menstrual periods as are those caused by pelvic lesions. It must be remembered, however, that some increase in pain may accompany menstruation in many cases of sacro-iliac backache.

Various lesions of the male genito-urinary system may cause confusion at times. Lesions of the kidneys and ureters usually cause pain that is localized higher and is referred to the scrotum. Lesions of the prostate gland and urethra, as a rule, cause perineal pain; this is rarely a symptom of lumbosacral or sacro-iliac lesions.

Patients who have osteoporosis usually are more than fifty years of age. It may be a manifestation of parathyroid disturbance, although, as a rule, this cannot be demonstrated. The condition usually is designated "senile osteoporosis." The findings are the roentgenologic changes of osteoporosis, often together with pathologic compression fracture. The disks, too, have undergone the rather characteristic ballooning seen only in this type of lesion. Pain is severe and usually is static in type.

Much has been written from time to time regarding the importance of congenital lesions of the lower vertebræ and sacrum. Spina bifida is usually of little or no significance with reference to the pain. In the presence of more extensive lesions, the pedicles and facets may be so involved as to produce disturbances in the stabilizing structures of the vertebræ, thus leading to traumatic or static changes in the lumbosacral joints which become painful. Such changes may be the underlying cause of spondylolisthesis, in which case too they are significant. In the extreme cases of spina bifida, with meningocele and myelodysplasia, the lesion is of course of primary importance.

Sacralization of the last lumbar vertebra or lumbarization by the first sacral vertebra often may be without any significance. If the sacralized transverse process is firmly united to the sacrum no movement can take place between the anomalous vertebra and sacrum. The intervertebral space is narrowed or obliterated and the facets are rudimentary or obliterated.

If only partial sacralization exists, so that movement may be present between the anomalous vertebra and sacrum, inflammatory processes may be set up which may produce symptoms.

### TREATMENT

The problem of treatment of low back disability is still of major importance. Various physicians have argued that this or that type of treatment is the appropriate one. The truth is of course that no one method is appropriate in all cases. Many types of treatment may help, many may even appear specific in some instances, but any one experienced in handling such cases knows that often he is disappointed.

In the acute case of back strain, in which there is a history of definite injury by twisting or falling or lifting, the most important part of the treatment is rest. In such cases, as a rule, much more headway will be made and recovery will be much more rapid if rest is given than if it is not. As a rule, it is difficult to persuade the patient to accept rest. Combined with rest several measures may be used, such as (1) firm strapping with adhesive tape across the pelvic and lumbar region, which acts as the simplest sort of splint; (2) placing of a scultetus binder about the pelvis and lower part of the abdomen may be of help if the patient is recumbent; (3) use of a fairly firm bed, preferably a "fracture bed," with boards on the springs and a firm hair mattress. There is little doubt in my mind that if more acute back strains were treated with complete rest in bed at first, there would be many less chronic back strains to treat.

Besides rest and fixation by strapping with adhesive tape or by a scultetus binder, heat and massage should help. Of course, when adhesive straps are applied, heat and massage cannot be used. If choice must be made between rest and adhesive strapping on the one hand and rest, heat and massage on the other hand, the latter usually will prove the more effective.

For recurrent, acute back strain, or "lumbago," more elaborate examination is essential. If obvious reasons for the pain can be found, such as skeletal changes, more radical treatment may be necessary. Usually in these cases, if ambulatory treatment is to be tried, a well fitted cloth corset or belt should

be made. Women will seldom wear a heavy canvas belt but usually will consent to wearing a cloth corset. Such a corset should, above all else, be carefully fitted. Many elaborate types of "surgical corset" are advertised. Their very complexity makes it difficult for the average patient to adjust them properly or to wear them comfortably. My own choice is a corset with laced back which should be applied and the laces drawn comfortably taut each time it is put on. In this way a comfortable, snugly fitting support is obtained. For men, a canvas belt, with or without a sacral pad, usually is the most satisfactory type of splint. Together with use of the corset, baking and massage should be carried out. Often a patient can procure some sort of radiant heat lamp and take such treatments at home, himself, if time or money does not permit his taking the treatments under the supervision of his physician or of such physiotherapists as his physician may recommend. Usually it will be necessary to continue such treatment for many months. After the pain has subsided, exercises should be commenced to rehabilitate the muscles which are bound to become more or less atrophied during the period of fixation. Such exercises should be simple, postural exercises designed to develop particularly the erector spinæ muscles and the gluteal muscles. An excellent substitute for such exercises is swimming. Probably no form of athletic diversion is more suitable than swimming and the patient who can swim, and who has the opportunity to do so, should continue with it until normal muscular strength has been restored; this will require several weeks.

For acutely recurrent attacks of what is commonly called sciatic scoliosis, manipulative treatment may be useful. In our experience at the Clinic, however, manipulative treatment rarely offers more than temporary relief when the backache is of the severely recurrent type. Mennell has described the various types of manipulation more commonly used.

In more severe cases, or in those which have become chronic, and in which pain is either continuous or severe, recurrent or disabling, much can be gained by treatment in hospital. Such treatment can serve a twofold purpose: first it offers the best conditions for the attempt to relieve the patient; second, it gives the physician a chance to observe the patient's

response to various sorts of treatments and thus allows him to get a better insight into the diagnosis and prognosis. Our routine treatment at the Clinic is as follows: (1) rest in bed with a fracture board on the springs and a firm hair mattress; (2) traction of 6 to 8 pounds (2.7 to 3.6 kg.) on each leg, employing moleskin adhesive tape or padded ankle cuffs; (3) some sort of support under the lumbar part of the spinal column either a pillow or a sling padded and counterweighted to a point which the patient can stand; (4) daily physical therapy, usually baking and massage alternating with diathermy until it is determined which type of treatment gives the patient the most relief; (5) epidural injections if there is sciatic pain and if relief of pain is not obtained by traction.

Usually on such a program the patient will complain of more pain for the first two or three days. About the fourth day some subsidence in the pain should be looked for if the patient is going to respond to such treatment. If pain is relieved and muscular spasm is decreased, the treatment should be continued ten days to two weeks, and then a gradual resumption of activity, wearing of a well fitted corset, continued rest and application of heat and massage at home should be prescribed.

Craig and I have reported elsewhere the details and results of such treatment. In a considerable number of such cases relief can be afforded by this combination of treatment.

If relief comes with the treatment but there is immediate recurrence of the pain on resumption of walking, more radical treatment must be considered. If skeletal changes, such as narrowed disks and changes in the facets exist and if conservative treatment has been given adequate trial without benefit, and if neurologic lesions have been excluded, surgical operation of some type may be indicated, probably fusion of the lumbosacral joint or of the lumbosacral and both sacro-iliac joints, depending on the findings on physical examination.

The original descriptions of the various types of fusion operation can be found in medical journals of the last ten years. The lumbosacral or sacro-iliac joints can be adequately secured by one of these methods.

It is our custom to keep the patients in bed, on a frame, for six weeks after operation, then to allow a minimum of activity until the end of four months when, if roentgenograms give evi-

dence of sufficient fusion, more nearly full resumption of activities can be permitted. At this stage, exercises to rebuild the weakened muscles should be instituted, again simple posture exercises, or swimming can be utilized.

Ober's fasciotomy has had a promising start in the surgical treatment of low back pain; whether the patients so treated will be permanently cured or not, remains to be seen. Details of the method will be found in the author's original article.

More recently, Mixter and Barr have emphasized the importance of avulsion of the intervertebral disks for back pain. This seems reasonable and logical. Time will show what is the proper method of handling these cases. In those cases in which neurologic signs and symptoms are found, excision of the offending disk, or at least of a portion of it, must be carried out. If, however, there are no real pressure symptoms it is questionable whether laminectomy is necessary in all such cases. Many patients may respond to lumbosacral fusion and some may require fusion as well as removal of the disk.



## TREATMENT OF FUNCTIONAL MENSTRUAL IRREGULARITIES

DELLA G. DRIPS

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OF the many clinical problems in gynecology, the treatment of functional menstrual irregularities has always held much interest and has become more fascinating with advancement in knowledge of the function of the glands of internal secretion. Physicians who are called upon to treat young women complaining of such irregularities must have some understanding of the physiologic and biologic problems involved and keep in touch with what is constantly being revealed by experimentation. To be able to use the newer hormone preparations intelligently one must have followed the experimental work leading to the isolation of the hormones and be familiar with their biologic reactions.

By a functional menstrual irregularity is meant some disturbance of the rhythm of the cycle or some variation in the normal duration or amount of menstruation due solely to a disturbance of the physiologic function of one or more of the glands involved in normal, regular menstruation. Of chief concern are the ovaries and the anterior lobe of the pituitary gland. Usually a functional menstrual irregularity dates from the onset of menstruation, or at least becomes evident during the developmental period. If a young woman can be carried along until the end of this period, that is, to the age of from twenty-one to twenty-three years, the normal physiologic function of the glands involved often finally asserts itself. Occasionally, functional disturbances first become evident after parturition.

Sterility or one-child marriages are very common in cases in which menstrual irregularities are not corrected, as would be expected. Before the newer methods of treatment came into

vogue, of a group of 144 married women who complained of an amenorrheic type of irregularity, with an average length of married life of 6.1 years, 53 per cent were sterile, and for the others the average number of pregnancies was 1.4. Of seventy-seven women who complained of functional metrorrhagia and who had been married on an average of 5.9 years, 44 per cent were sterile, and the average number of pregnancies among the others was 1.6.

Functional menstrual irregularities may be divided into two types: (1) the amenorrheic type, the patient complaining either of skipping periods, a tendency to longer intervals between periods, or of less flow or a shorter period, or of all of these symptoms; and (2) the metrorrhagic type, the patient complaining of a shortening of the interval between periods or of more prolonged or profuse periods often with continuous bleeding. Both types are assumed to be due to a hyposecretion or complete absence of one or both ovarian hormones: the amenorrheic type to a hyposecretion or absence of both the estrogenic and the luteal hormones of the ovaries, and the metrorrhagic type usually to a hyposecretion or absence of the luteal hormone. It is not unusual, however, to have continuous bleeding associated also with an absence of estrogenic hormone in the urine and an atrophic type of uterine endometrium.

In the amenorrheic type of irregularity the uterus tends to become smaller, and the endometrial change over that of the resting stage depends on the amount of hormones present. There may be very little proliferation and little differentiation premenstrually. The uterus of the metrorrhagic woman usually is entirely normal in size, or even larger as a result of the sufficient estrogenic hormone present. Proliferation of the endometrium occurs and often is much exaggerated over normal, but the secretory or differential phase is not reached. Bleeding may occur from dilated sinuses through ruptured capillary walls, but this is not true menstrual bleeding. Luteal hormone which brings the endometrium into the true secretion phase is lacking.

Either of the two glands chiefly concerned with menstruation, the ovaries or the pituitary (anterior lobe) may fail and an irregularity ensue. The type of irregularity in each case may be very similar although with primary pituitary failure,



the rhythm of the cycle is likely to be more disturbed. The patient, however, as a whole presents a different clinical picture in each case. Those belonging to the hypopituitary group are usually overweight and their basal metabolic rates are below normal; they usually complain only of a tendency to obesity and sterility. The women with ovarian hypofunction are usually normal or underweight, their basal metabolic rates tend to be normal and, in addition to sterility, they usually have numerous complaints associated with the menses: soreness of the breast before the periods, a migraine type of headache before or at some time during the period, menstrual pain of either the uterine or ovarian type before or with the period, low backache, aching in the thighs, gastro-intestinal complaints such as gas and bloating, increased nervous irritability before periods, and even vasomotor disturbances, especially hot flashes between or with the menses. All of these symptoms of ovarian failure are noticeable in most women with the onset of the menopause period. It is believed that they are not directly due to a lack of the ovarian hormones, but to an excess of anterior pituitary gonadotropic hormone, as they are not present in primary pituitary hypofunction with secondary ovarian failure. These are not only clinical assumptions, but are borne out by determinations of the content of estrin and prolan in the blood and urine in these cases. In primary ovarian failure the content of estrin is found to be lower than normal, and prolan is normal or in excess, depending on the degree of ovarian failure. In primary pituitary failure, both estrin and prolan are lower than normal.

One small group into which some cases of amenorrhea fall might be mentioned here. In such cases it would seem as if some unknown factor were responsible for the amenorrhea. The patients are normal in every way, blood and urinary hormones are present within normal limits, and the uterus is of normal size. These women may become pregnant without menstruating.

It would also not seem amiss here to say more about the methods of determining estrin and prolan in the urine, as one is often dependent on these determinations in deciding which gland's failure is responsible for the patient's complaint. By urinary estrin I have reference to an ovarian hormone found

cyclically in the urine of every woman who is having menstrual periods. It is the hormone of the ovaries that has to do with maintenance of the size and turgor of the accessory organs: the uterus, vagina, external genitalia and breasts. It induces cyclic proliferation of the endometrium of the uterus, and in sufficient quantities in the blood stream suppresses pituitary function. In the mouse and rat this hormone induces the changes in the uterus and vagina that are incident to the state of heat, or estrus; hence its name. At the time of heat there is desquamation of pure cornified epithelial cells from the vaginal wall into the lumen, and the obtaining of such cornified elements alone in a vaginal smear from a castrated adult animal is the positive test for the presence of estrin in any test material injected into the animal. For a determination of urinary estrin it is therefore necessary to extract the hormone from the urine and to inject it into castrated, adult female mice or rats, and, by taking vaginal smears, to test for the estrus reaction, which is the pure cornified smear.

An attempt is made at the Clinic to make determinations as quantitative as possible. The urine is collected for twenty-four hours, 700 c.c. of pooled urine being used. The hormone is extracted and carried over finally into 10 c.c. of olive oil. This is injected in varying doses into from three to six test animals, three injections being given at twelve-hour intervals and vaginal smears being taken twice daily for four days. The smallest total amount of olive oil containing the hormone which when injected into a single rat produces the estrus reaction, as evidenced by the cornified vaginal smear, is then noted. From this is calculated the total rat units of estrin in the twenty-four hour specimen of urine. The amount of estrin excreted in twenty-four hours varies for each day in the normal cycle of every woman; it also varies in different individuals, so that one has to study the estrin excretion of many normal women for several cycles in order to establish graphs of normal estrin content. The greatest excretion of estrin in the urine in any single twenty-four hours occurs midway between menstrual periods. The values for excretion are lowest near the menses. The normal values for the midcycle vary in our series, with the Kurzrock method described here, between 14 and 30 rat units. At present we at the Clinic are using the Smith method,

which extracts both the free and combined estrin, and the values run about twice as high (Figs. 46 and 47).

Prolan in the urine of nonpregnant women is the true anterior pituitary gonadotropic hormone. It can produce in the ovaries of immature rats follicle ripening or luteinization, depending on the amount of hormone; in the great proportion

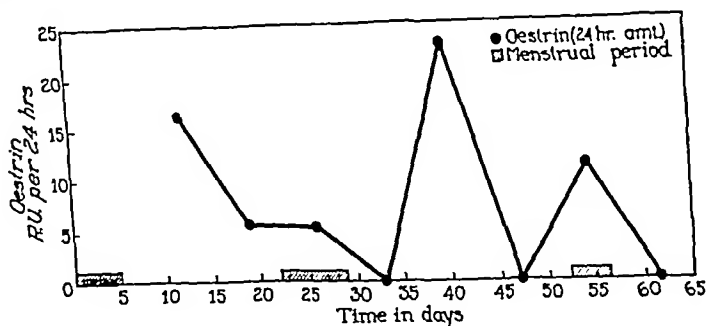


Fig. 46.—Estrin in the urine of a young woman with apparently normal menstrual cycles. A twenty-four hour specimen of urine was obtained once a week.

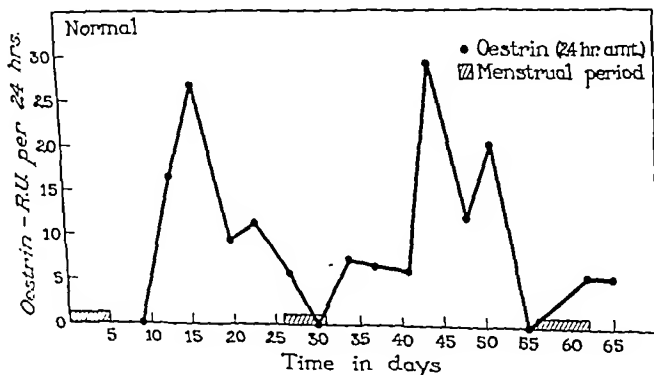


Fig. 47.—Estrin in the urine of a young woman with apparently normal cycles. A twenty-four hour specimen of urine was obtained every third day.

of cases, however, with present methods of extraction only follicle stimulation is obtained. At the Clinic we have not attempted to make our prolane determinations quantitative. We attempt by two different precipitation methods to determine only if prolane is present in excessive amount or if it is present in small or nearly normal amounts. In certain cases of dys-

function, when partial or complete ovarian failure is present, prolactin will be present in the urine in excessive or greater than normal amounts. This is what occurs, of course, in the menopause, so if we suspect ovarian failure and excess pituitary function, we use the Aschheim-Zondek alcohol precipitation method: The patient is requested to bring in the early morning specimen of urine, 60 c.c. being necessary for the test. Three or four times this volume of alcohol is then added and prolactin is precipitated, all of the precipitated prolactin finally being obtained in a concentrate of 12 c.c. This amount is then divided and injected into three to six immature female rats, about twenty-one days old and weighing from 27 to 30 gm.—litter mates if possible. Six injections are given at intervals of twelve hours; at the end of 100 hours the rats are killed, the uterus and ovaries are observed grossly and weighed, and the ovaries are put into a fixative, and are later embedded in paraffin, cut and stained. Cross sections of the ovaries of animals that have received injections are then compared with those of a control animal, that is, if possible, a litter mate. We look for evidences of follicle stimulation (increased maturity of any follicles, and an increase in the number of medium size and large follicles, with the formation of antra) and normal corpora lutea; and then compare the weights of ovaries and uterus of the animals that have received the injection with those of the control. These are the criteria for the presence of prolactin in the test extract. The smallest amount of this extract sufficient to produce stimulation represents at least 66 rat units of prolactin to the liter, or 1,000 c.c., which means that prolactin is present in amounts greater than normal, which at most would probably be not more than 16 rat units. When we wish to test for normal amounts, or to see if any prolactin at all is present, as in cases of suspected pituitary hypofunction, we collect 1,000 c.c. of urine. The prolactin is then extracted from this by a method which precipitates much more prolactin than is possible with alcohol. (Levin's tannic-acid precipitation method has been most satisfactory.) The biologic assay is the same.

As a rule, with either of these methods one sees only follicle ripening. The luteinizing hormone, or at least the pituitary gonadotropic hormone, is present in amounts too small to in-

duce formation of corpora lutea. To my knowledge, at no time during the cycle of a normal woman has prolan been found in amounts greater than 25 rat units to a liter, and usually it is not present in determinable amounts except at two periods in the cycle: at some time during menstruation, and again near the middle of the cycle. It is therefore evident that, if possible, it is best to collect the urine for determination of both

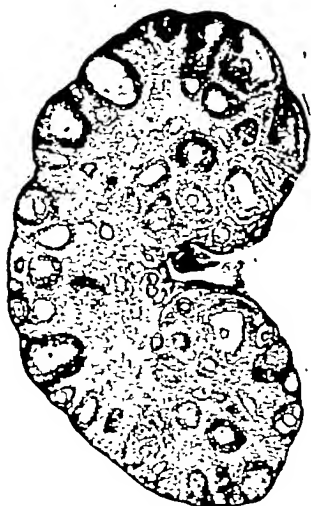


Fig. 48.

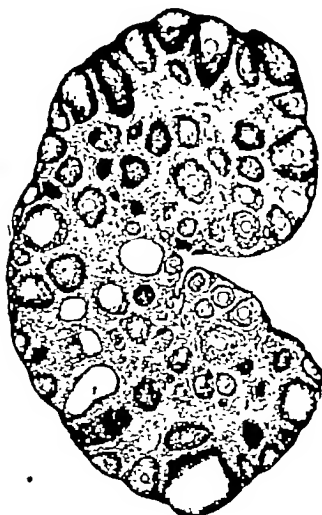


Fig. 49.

Fig. 48.—Cross section of ovary of a normal rat twenty-one days old.

Fig. 49.—Cross section of ovary of a rat twenty-one days old after injection of a urinary precipitate obtained with tannic acid. Levin method for demonstrating prolan present in normal amounts or above. Some follicle stimulation is evident. The urine was obtained from a girl, twenty-one years of age, who complained of irregular periods and severe dysmenorrhea. The failure here is assumed to be ovarian as the pituitary response is normal.

estrin and prolan midway between periods, or about two weeks after the onset of the period, and always the first day of the last menstrual period before the collection of the urine should be noted for convenience in judging values (Figs. 48-51).

Most workers have asserted that it is of no diagnostic aid to have solitary or weekly values of urinary estrin and prolan, but that determinations should be made daily, or a determination should be made on each three-day amount of urine over

several weeks. This is probably true when one is trying to determine in a case of primary amenorrhea or amenorrhea of many months' duration whether any ovarian or pituitary function is present, but even here single positive values are very helpful. Whenever possible several determinations are made in order to get a positive value and to obtain some evidence that a cycle is still present. The chief reason, of course, for

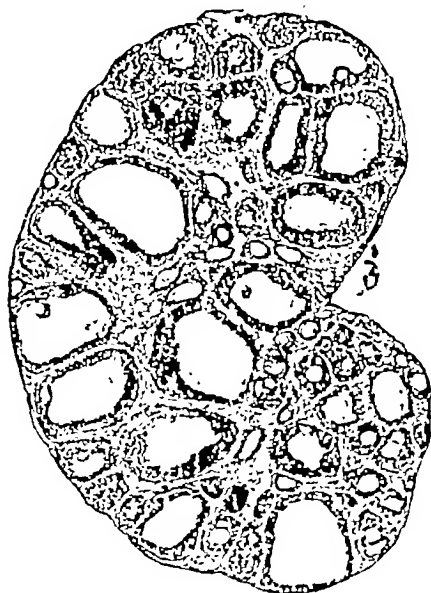


Fig. 50.—Cross section of ovary of a rat twenty-one days old after injection of a urinary precipitate obtained with alcohol. Aschheim-Zondek method for excess prolactin. The urine was obtained from a woman, thirty-three years of age, who had not menstruated for nine months. She was having some hot flashes. Marked follicle stimulation here is evidence of excess pituitary function and ovarian failure. There was no estrin demonstrable in a twenty-four hour specimen of urine.

any investigation in these cases of dysfunction is to determine, if possible, where the failure lies—whether there exists a pituitary or ovarian deficiency. Endometrial biopsy is also of aid in these cases, but occasionally the uterus becomes atrophic and stays so even after the cycle gets to going again; the endometrium is reported as atrophic, and one would need to interpret this to mean that no cycle was present when, very often,

estrin is found to be present in the urine, making the prognosis much better.

I have recently studied a group of cases, sixty-two in all out of a total of 109, in which determinations of urinary estrin and prolan were made because of some functional menstrual



Fig. 51.—Cross section of ovary of a rat twenty-one days old after injection of a urinary precipitate obtained with tannic acid. Levin method for demonstrating amounts of prolan normal or above. The urine was obtained from a girl, twenty years of age, who had never menstruated. The marked luteinization is evidence of a high content of urinary prolan, which indicates excess pituitary gonadotropic function. A twenty-four hour specimen of urine was negative for estrin. Only a tiny uterus was palpable, and absence of the ovaries was suspected.

disturbance. These sixty-two women had complained of scanty flow, although their periods had been regular; all but thirteen of them were married and complained of sterility. Thirty-nine of the sixty-two women had various symptoms associated with the scanty flow, chief of which were headache and dysmenor-

rhea. They complained in addition of soreness of the breasts a week before the periods and of a bearing-down discomfort in the pelvis as though the period were coming on, of aching in the lower part of the back, nervousness and irritability, sleeplessness, and a feeling of tenseness, and so forth. Four women were intensely nervous, and had hot flashes before their scanty periods and much nausea and pain with the flow. These women with the severest symptoms we expected might have excess prolactin in the urine and very low values for estrin as we thought that, clinically, these cases represented the most outstanding examples of ovarian failure. Prolactin was found in excess in the urine, but the values for estrin were normal or higher than normal. It appears as if the pituitary, once getting stimulated by a lack of estrin, keeps up its overfunction until the level of estrin gets sufficiently high to suppress it; or we may in some cases be dealing with a true hyperpituitary gonadotropic function. We are at present continuing our investigations in this group of cases. This study served to show the value of hormone determinations. There is no doubt that many of the menstrual abnormalities are due to pituitary hyperfunction rather than to a real lack of estrin. Such symptoms are sore breasts, headache and vasomotor instability with hot flashes. All the women in this group without associated symptoms had amounts of prolactin in their urine too small to be detected by our technic.

Every young woman who complains of a menstrual irregularity is entitled to a thorough general examination (the history of the irregularity being taken carefully), particular attention being paid to her general build, the development of her breasts and external genitalia and to the pelvic examination, with special reference to any local pathologic changes and to the size of her uterus and ovaries. Cystic ovaries are very common in these women with functional disturbances. A roentgenogram of the sella turcica should be made, the basal metabolic rate, and amounts of estrin and prolactin in the urine should be determined, and endometrial biopsy should be performed, when feasible.

When women complain only of sterility, and in borderline cases in which the menstrual periods are fairly regular and normal, endometrial biopsy just before menstruation is invaluable. This alone will tell whether one is dealing with any



deficiency of the ovarian secretions; and, if the uterine endometrium is of the normal premenstrual differentiative type when it should be, the cause of the sterility is probably not endocrine. In cases in which bleeding occurs, it is often necessary to do a curettage for diagnosis. This offers endometrium for study when no organic cause is found for the metrorrhagia. Pelvic exploration has at times to be resorted to in order to rule out ovarian neoplasms or endometrial tumors.

The purpose of treatment in all these cases is, of course, to try and establish at least as normal and as regular menses as the patient considers normal for herself. Essentially, irregularity of menstruation is any deviation from what the patient herself considers normal.

The treatment of the amenorrheic type of menstrual irregularity depends on whether failure is primarily pituitary or ovarian. In the hypopituitary group, the first consideration is the usual overweight. A reduction diet high in vitamins and with sufficient protein is given. As the basal metabolic rate is usually less than  $-10$ , the next consideration is elevation of the rate to around  $-5$ , with an attempt to hold it there indefinitely. If after from three to six months thyroid medication alone does not establish menstruation or correct the irregularity, low-dosage irradiation of the pituitary gland and ovaries is considered.<sup>1</sup> Irradiation is especially considered when one is dealing with amenorrhea of more than six months' duration. In this type of case, low-dosage roentgen therapy offers a good chance (80 per cent) of bringing on a menstrual period, which usually comes on directly after the treatment or five weeks following. When the first treatment is not effective, it is repeated if possible in three months. Whenever it is possible to employ thyroid medication, its continuous use certainly appears to help keep the cycles going.

In cases in which the amenorrhea has not been present more than four or five months, it is possible at times to bring

<sup>1</sup> For the treatment of ovarian dysfunction, we at the Clinic are now irradiating one field over each temporal region, centering over the pituitary, and one field over the front of the abdomen, centering over each ovary. The following technic is used: 200 kilovolts, 10 milliamperes, 0.75 mm. copper and 1 mm. aluminum filters, 50 cm. distance, for five minutes. This represents approximately one-sixth of a skin erythema dose.

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on a period by intramuscular injections of a preparation of the female sex hormone (progynon-B, 5,000 to 10,000 International units), an injection being given every fourth day. Usually after three or four injections a period ensues; it may, however, ensue after one injection, which is the reason for waiting four days between injections. The next month, injections are repeated on the same days and another period will ensue. After three or four months' treatment the cycle carries on of itself. Single large doses of estrogenic hormone apparently stimulate the pituitary gland. Thyroid medication has been very valuable in straightening out minor irregularities in these cases and especially in those in which sterility is a chief concern. Minor menstrual irregularities in this group treated before the uterus has become too atrophic respond rather easily. The uterus undergoes much more rapid atrophy in cases of amenorrhea of primary pituitary hypofunction than in those in which it is primarily of ovarian origin. For this reason treatment should be begun three months after the onset of the amenorrhea. The earlier treatment is begun the simpler it will need to be, because after marked atrophy of the uterus occurs any form of treatment may be of no avail.

In cases of primary ovarian failure one is confronted not only with the problem of the menstrual irregularity and the associated sterility but, in addition, with the train of symptoms associated with such failure. In considering therapy, then, one strives not only to reestablish regular, normal cycles, but also to relieve the patient's symptoms. The basal metabolic rate in these cases is usually within normal limits, so it is seldom possible to employ thyroid medication; if only small doses are possible, thyroid medication seems to be of value. In cases of amenorrhea of more than five months' duration, low-dosage roentgen irradiation of the ovaries is of value, and it is in this group that periods are frequently reestablished after long intervals because the uterus does not become so atrophic. Values for estrin are not as low as in pituitary amenorrhea, in which pituitary stimulation is lacking. In one of our cases, that of a woman of twenty-six years, the menses were reestablished after seven years of amenorrhea, the first period occurring five weeks after low-dosage roentgen irradiation of the ovaries and pituitary gland. We do not advise irradiation of the pituitary

in the group of cases of primary ovarian failure when the urine contains prolan in excess amount or when the patient is having hot flashes, as such a patient's pituitary gland is making a good physiologic response. Otherwise there seems to be no untoward effect from giving low-dosage roentgen treatments over the pituitary gland and the procedure appears to be beneficial. Increased pituitary function is the normal physiologic response to ovarian failure and often relieves it; therefore it is not unreasonable to stimulate a pituitary gland that has not itself responded.

Emmenin (complex type) will often apparently stimulate the ovaries to greater secretion of hormone and indirectly influence the uterus, and in this way relieve the dysmenorrhea which is associated with partial ovarian failure. Emmenin has been found especially valuable in the treatment of younger women whose dysmenorrhea seems to be on a basis of ovarian dysfunction. It should be begun about the seventh day of the cycle, counting from the first day of the last menstrual period, and should be taken daily until about the twenty-fourth day. Both theelin and emmenin have been very effective in the relief of menstrual headache, and there has seemed to be some relief from grand mal attacks when these have a tendency to occur only with the menses. Acne flaring up with menses has been influenced by theelin and emmenin, and also by injections of a gonadotropic hormone of pregnancy urine (antuitrin S; 200 rat units or 2 c.c. being given every other day for eighteen injections according to Lawrence). As yet it is not known just what histologic or pathologic changes occur in human ovaries on injection of antuitrin S, and therefore much caution should be used in prescribing it. Theelin therapy would seem to be safer. Urticarias which appear to be related to the menses are frequently benefited by theelin therapy. Urticaria seems to be directly related to a lack of estrin in the circulation as it occurs in ovarian hypofunction, either primary or secondary to pituitary failure.

It would seem as if anything which improves ovarian and uterine circulation will help in improving the secretory activity of the ovaries. Vaginal Elliott treatments and diathermy may be at times of benefit when low-dosage roentgen apparatus is not available. Low-dosage roentgen rays probably only pro-

duce their effect by causing a state of congestion in the ovaries. Frequently a combination of treatments helps more than a single type of treatment only. Low-dosage roentgen irradiation of the pituitary gland and ovaries, followed by the administration of emmenin or theelin, seems to give better results than either alone. When theelin therapy is employed, it is better to try and simulate the physiologic cycle and then stop such treatment four or five days before an expected period; otherwise, the period may be postponed and this is psychologically bad for the patient. Continued treatment may not do this, but it very occasionally does.

When one is trying to control severe migraine headaches or grand or petit mal attacks which occur only with the menses, it is better to keep treatment continuous even though there may be some postponement of the period, for two or three months at least. The period is usually only delayed a few days to a week. The continuous use of theelin evidently keeps down pituitary stimulation, so that when it comes it is milder and attacks are not precipitated. The attacks seem to correspond to periods of excess pituitary stimulation, as tests for excess prolan, according to the alcohol precipitation method of Ascheim-Zondek, are positive at these times. No doubt many other factors are present as well, but it appears as if an endocrine imbalance exists and that theelin has some influence on the frequency and severity of the attacks.

In spite of the fact that in these cases of primary ovarian failure one may occasionally get a startling response to low-dosage roentgen therapy after several years of amenorrhea, because one is dealing apparently with a cycle in the uterus as well as in the other glands involved, that is, just a little subnormal, the prognosis with roentgen therapy in cases of primary hypopituitary amenorrhea as a whole, and especially in those in which the amenorrhea is of less than two years' duration, is better than that for cases of primary ovarian amenorrhea. In a recent series of carefully diagnosed cases of primary ovarian amenorrhea of more than six months' duration, only seven of nineteen patients (36.7 per cent) responded to roentgen treatment, which means that periods were reëstablished—in one case after amenorrhea lasting seven years. One woman became pregnant of the four married women who

were treated. Twelve of fifteen (80 per cent) patients of the group with primary pituitary amenorrhea responded to low-dosage roentgen irradiation and thyroid medication, and one of the three married women in this group became pregnant.

Cases in which women have shorter periods of amenorrhea (less than six months) and minor irregularities we class as being those of ovarian dysfunction of the amenorrheic type. In this group thirteen women whose amenorrhea seemed to be related to the pituitary were given low-dosage roentgen treatments. Only one failed to respond and there were four pregnancies among eight married women. One out of nine women with minor menstrual irregularities considered to be due to partial ovarian failure failed to respond and there followed two pregnancies among five married women in this group.

A much higher percentage of improvement was noted among those patients with primary ovarian amenorrhea (more than six months) for whom all types of therapy were tried than among those who had received low-dosage roentgen therapy alone. Fourteen of twenty-one patients (66 per cent) had their periods reestablished. This improvement was brought about by a combination of treatment, giving doses of theelin in oil, 1,000 to 2,000 rat units daily for periods of three weeks in addition to low-dosage roentgen therapy and, when possible, thyroid medication. Theelin in oil has definite value in these cases for it alleviates the symptoms associated with ovarian failure. Injection of theelin in oil has not been tried consistently in the treatment of the hypopituitary amenorrhea in spite of the assumption of some that it might increase the size of the uterus and make it more amenable to subnormal amounts of ovarian hormone in the circulation.

In the group of cases of primary pituitary failure in which patients were treated by all forms of therapy the percentage of reestablished menses after six months of amenorrhea was 69 per cent. As noted before, the majority of patients were treated by thyroid medication and low-dosage roentgen irradiation. The failures in this group occurred when thyroid medication alone was employed or a reduction diet and vitamins alone. Treatment by vitamins alone, while often being sufficient to care for minor menstrual irregularities, is not sufficient to bring on periods after six months of amenorrhea. The same

can be said for thyroid treatment alone, though occasionally it has been very effective.

Of patients with minor irregularities of the primary ovarian type who received all forms of treatment, twenty-nine of thirty-five improved (82 per cent), and of those with minor irregularities of the primary pituitary type, thirteen of sixteen improved (81 per cent). Rapid atrophy of the uterus in the latter group probably is a factor here. It has at times been impossible to overcome this with our treatments. This has led us at the Clinic to treat every woman after three months of amenorrhea if she belongs in this group. Haines and Mussey reported a series of fifty patients with amenorrhea who were treated with desiccated thyroid alone; as a result 58 per cent had normal or nearly normal periods. The average duration of the amenorrhea among those who improved was 9.5 months. Two patients with amenorrhea of four and five years' duration, respectively, had their periods reestablished. No attempt was made in this series to distinguish between primary pituitary and primary ovarian failure.

The metrorrhagic type of menstrual irregularity is probably now the most satisfactory type to treat. The choice of treatment here depends on the age of the patient, the severity of the bleeding and the length of time from the onset of the irregularity. Considering these factors, the most conservative measures possible are always tried out first, especially for younger women. If the metabolic rate is below  $-10$ , it is often very beneficial to give sufficient desiccated thyroid to raise it to  $-8$  or  $-5$  and to hold it there consistently. Patients are then given a diet especially high in vitamins, iron and calcium. The normal weight for the patient is always considered in outlining the diet. If patients cannot drink three glasses of milk a day, calcium lactate is added. This should always be dissolved in some hot liquid, and it is usually given in amounts of 1 drachm (4 c.c.) three times a day. Calcium seems to help at times even when the value for blood calcium is normal. Injections of parathyroid hormone which raises the level of calcium in the blood have been used abroad and have been reported to be of value. In addition, sistomensin (Ciba Company) is still used considerably because it can be given orally and seems to contain sufficient active luteal hormone to be



effective in checking the flow, evidently by changing the endometrium over into the differentiative or secretory type. Sisto-mensin (Ciba Company) contains some estrin also, but it is used in these cases for its content of luteal hormone. It needs to be given in doses of 2 tablets three or four times a day, preferably on an empty stomach. It is best to begin it ten days before an expected period and continue it until the profuse flow is over. If the condition is not controlled in this way, a preparation of luteal hormone, proluton (Schering Corporation) is given intramuscularly. Unless the flow is very severe, ampules containing  $\frac{1}{25}$  rabbit unit are used. One ampule daily for five to seven days will usually suffice to check the flow. By the end of this time the bright red flow will change over into a dark menstrual type and cease after three or four more days. If the periods are fairly regular an ampule of proluton is given every other day for a week prior to the period and for the first five days of the flow. At present proluton is obtainable also in ampules containing  $\frac{1}{8}$  rabbit unit and 1 rabbit unit, but it is not often necessary to use these dosages. Only a very small amount of active luteal hormone seems necessary.

In case of too frequent periods a preparation of luteal hormone given between periods will often postpone the event. If bleeding has been present for several months, there is usually such thickening of the endometrium that the hormone preparation cannot effect a change in it, so it is better to curet it out gently and then, with the aid of the hormone or hormones which are lacking, to attempt to build up a more normal endometrium. Curettage offers a chance to study the endometrium. When both estrogenic and luteal hormones are lacking the endometrium will be atrophic. It is more common for it to be of the hyperplastic type owing to a lack of luteal hormone and an overabundance of estrin.

It is very important in these cases to rule out any blood dyscrasia. At times, when the patient has become markedly anemic, it is necessary to give a blood transfusion. We rely on a diet high in iron rather than giving iron medication such as ferric ammonium citrate which, in our experience, is apt to increase the bleeding. This can be given, when necessary, between periods of bleeding. Severe hemorrhages in these cases are not the rule, and it is often surprising how much and how

long a patient can menstruate without getting markedly anemic. Ordinarily activity does not usually increase the bleeding as the patients themselves will usually declare, and it is best for them to be allowed to carry on their usual activities. Excitement or competitive sport will in many cases initiate or increase the bleeding evidently by stimulating the pituitary gland, and should therefore always be avoided. Rest in bed and ice applied to the lower part of the abdomen, in addition to the calcium and luteal hormone will soon control an increased amount of flowing. There are certain cases in which it would appear as if the dysfunction were primarily pituitary, and in these cases patients respond well to injections of antuitrin S, 200 rat units (2 c.c.) being given every day or every other day during the same period as mentioned for proluton. Great caution must be exercised when this treatment is given, as noted before.

When bleeding persists after all these measures have been tried, intra-uterine radium treatments prove very effective. The dosage depends on the age of the patient. For a patient aged eighteen years, 150 mg. hours is used; for a woman thirty years of age, 350 mg. hours. The effect of the radium may not be apparent for six weeks. After this, menstruation usually ceases for two or three months, during which time the patient regains her strength and overcomes the associated anemia. When the periods return, they tend to be more regular and the duration and amount of flow are more normal. Other methods have been tried, but none has so far been found more effective. With the doses mentioned, no patient in our series ceased menstruating for more than three months, and of twenty-four women treated in this way, twenty-two were having fairly regular and normal periods at the end of one year. The other two were not benefited.

Recently, snake venom has been tried in a small group of cases. Watkins and Mussey have reported their experience with snake venom in seven cases of functional metrorrhagia. The injections were continued for several months, the average time being about eight months, although improvement usually occurred within one or two months after treatment was started. None of the seven patients failed to improve, although one received the venom twice weekly in dose of 1 c.c. for a period

of four and a half months before the menstrual flow returned to what was considered normal. Certain of these metrorrhagic patients also have a tendency to bruise easily, though no definite blood dyscrasia can be demonstrated by any known methods. It would seem as if such patients were particularly suitable for venom therapy.

### CONCLUSIONS

An attempt should be made to classify every functional menstrual irregularity with regard to the glandular dysfunction involved. To do this it is necessary to have in mind a history of the irregularity from the onset and a clear-cut impression of the physical characteristics of the patient and especially of the pelvic organs. Several basal metabolic rates, determinations of the urinary estrin and prolan made at three-day intervals for a month at least and the changes in the endometrial pattern over the same period from biopsy specimens usually fix the diagnosis.

We find that the majority of all functional irregularities fit into two great groups; those secondary to primary pituitary failure and those due to primary ovarian failure. Either an amenorrheic or a metrorrhagic type of irregularity may result from a lack of one or both hormones of the ovary. In primary pituitary failure the basal metabolism is lowered and this seems also to be a complicating factor in the menstrual irregularity. In the treatment in this group, raising the metabolism is a primary consideration but this alone will usually not straighten out many of the irregularities. In addition, stimulation of the pituitary by low-dosage x-ray therapy insured the best results. In primary ovarian failure, it is necessary to improve the condition of the ovaries. The aim is to increase the circulation. This has been done by some form of heat or by low-dosage x-ray therapy. When it is not possible to make the ovaries secrete more hormone it must be supplied to meet the needs of the individual. Primary ovarian failure has associated not only the physical symptoms of faulty function of the dependent accessory organs but all of the nervous and mental phenomena of an unstable vasomotor mechanism. These symptoms are not all directly dependent on a lack of ovarian secretions but to a

compensatory excess of pituitary secretion as they are not present in primary pituitary failure. The good results in the treatment of these cases are so dependent on an accurate diagnosis of the primary gland failure that every means possible to make clear where the deficiency lies and how much deficiency we have to deal with is most essential.

## PROBLEMS OF THE MENOPAUSE AND RELATED THERAPY

DELLA G. DRIPS

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It was Zondek who first put treatment of the menopause on a logical basis. He studied the blood and urine of women at the climacteric with regard to the amounts of anterior pituitary gonadotropic and ovarian estrogenic hormone present. As a result of these studies he divided the menopause into three periods:

### PERIOD 1

This is the period of more frequent or excessive menstruation, when a higher than normal amount of ovarian estrogenic hormone is found in the blood and urine. It is now considered to be evidence of the failure of development and function of normal corpora lutea. The pituitary stimulus can no longer bring about normal rupture of the follicle and normal luteinization of the granulosa cells. Instead of rupturing, the follicle may become abnormally distended with fluid containing an unusual amount of estrogenic hormone. So-called cystic degeneration of the ovaries occurs in this way. An abnormal amount of estrogenic hormone is secreted into the blood and urine by these cystic follicles. Partial luteinization of the granulosa cells may occur, but such a follicular structure, even though it may become partly luteinized, cannot produce the same amount of luteal hormone as a normal corpus luteum. An imbalance exists between the estrogenic and luteal hormones of the ovaries. This evidence of disturbed function is reflected in the endometrial changes which take place in the uterus. Instead of the normal secretory, late differentiative endometrium of the premenstrual phase, we find an endometrium now known to be representative of luteal failure—a late proliferative type of endometrium which may show cystic

degeneration. The uterus is often found to be larger and softer than normal. This, too, is the result of excessive amounts of estrogenic hormone. In determining the values for estrin in these cases one must remember that the highest values will be obtained about midway between the menstrual periods, as in normally menstruating women, and low values, which seem to contradict the foregoing assumption, may be obtained during the bleeding periods.

**Treatments.**—The treatment of this first period of the climacteric has to do with control of increased menstrual bleeding. As this is only a symptom and may quite as well be evidence of early malignancy of the body of the uterus, curettage is in order to rule this out. If scrapings reveal nothing organically wrong and the endometrium shows the typical proliferative picture, a preparation of luteal hormone may be tried in an effort to control the increased and prolonged flowing. At times, sistomensin (Ciba Company, Inc.) given orally, two tablets three or four times a day, is sufficient. Sistomensin contains both the estrogenic and luteal hormones. It is known that very small amounts of luteal hormone may be sufficient to effect the final premenstrual change in the endometrium. Sistomensin is used in these cases for its content of luteal hormone. Administration must be begun at least a week before the expected menstrual period and be continued through until the flow ceases. Calcium lactate, 1 drachm (3.8 gm.), three times a day after meals, dissolved in some hot liquid, seems to enhance the effect of sistomensin even though the patient's blood calcium is normal. When sistomensin given orally does not suffice, proluton, a standardized preparation of luteal hormone (Schering Corp.) is given intramuscularly. One ampule, containing  $\frac{1}{25}$  rabbit unit, is given daily for five days prior to menstruation and for the first five days of the period when this is deemed necessary. Ampules containing  $\frac{1}{3}$  and 1 rabbit unit of proluton per cubic centimeter are also available and can be used when necessary. Preparations of ergot do not help much. If menorrhagia continues for more than five or six months, and if the hormone preparations do not suffice and the patient's hemoglobin begins to drop, radiotherapy is used. Women of this age are urged to have sufficient intra-uterine radium or pelvic roentgen treatments to stop the menses.

## PERIOD 2

This is the period of vasomotor disturbances. During this period there is further evidence of ovarian failure. There are fewer granulosa cells of the follicles to respond to pituitary stimulation. A decreasing amount of estrogenic hormone is secreted by the follicle. The uterine endometrium reaches only an early proliferative phase, or may show no evidence of regeneration. The uterus is found to be smaller than normal. The menses become farther apart and less in amount, finally ceasing altogether. A rhythm is usually maintained to the end. The menses will occur, instead of every twenty-eight days, at multiples of this interval—every two, three or four months. This is significant in that it emphasizes bleeding which occurs at irregular intervals as denoting some organic abnormality. The vasomotor disturbances reach their height during this period. They may be present for some time before the menses cease tending to occur at the midinterval and during menstruation. It is during this period also that the blood and urine of the patient begin to show an excess of anterior pituitary hormone, which increases in amount with the ovarian failure. The amount of estrin in the blood and urine decreases.

**Symptoms.**—The increased menstrual molimina at this age are often most distressing. Women who have never had any soreness in the breasts prior to menstruation will complain of it during this late period of their menstrual life. They can often predict the onset of a menstruation seven to ten days after soreness is present. ¶

Another characteristic complaint is headache of the migraine type, which comes either just before, during, or after menstruation. If the patient has always had headache with the menses, it becomes much aggravated. Many women have headaches only during this age period. After the menses cease, most women are free of this migrainous type of headache.

Patients also complain of nervous instability; they get annoyed easily, become fatigued easily, and are easily stimulated or depressed for a week or so before their menstrual periods. Many women have increased discomfort with the menses as these become scantier and farther apart.

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Probably, for the majority of women, this age period be-

fore the final cessation of the menses is the most distressing one of the whole climacteric. Partial ovarian failure and compensatory, excess pituitary function lead to complaints of a physical nature, such as soreness of the breasts, headache, aching of the back and thighs and dysmenorrhea, and these, together with the beginning mild vasomotor disturbances are repeated with each menstrual period and are incapacitating and exasperating.

When the menses finally cease, vasomotor disturbances often become more severe for a time, usually for six to eight months, and then either subside entirely or continue to come and go with varying severity for several years. There may be some ovarian function sufficient to bring on these rhythmic symptoms for some months after any external evidence of menstruation is present, as studies of the hormones in blood and urine during this period have proved.

It would not seem amiss here to describe in detail what is meant by a "hot flash." Many clinicians are not familiar with the sensations that accompany such a vasomotor phenomenon. German physicians term the phenomenon a "vasomotor wave." The patient most often notices the sensation first in the epigastrium. This is the aura, and with it comes to some a feeling of oppression as though something were going to happen, or a feeling of light-headedness or faintness; a peristaltic movement of the bowel is often sensed and may be followed by the passage of gas from the rectum. At the same time the wave seems to rise upward through the chest to the neck and head. The patient may be conscious of palpitation of the heart or of a sense of air hunger, and take one or two deep breaths; her head feels as if it were going to burst. Then the sense of heat comes, first to the face and neck, next spreading to all parts of the body; finally moisture is felt in the palms, soles, axillæ and about the trunk. At times sweating may be so profuse as to drench the undergarments or make a change of night clothes imperative. Any or all of these sensations may be minimized or exaggerated in the individual case. Zondek stated that with the most intense stimulation there may be associated alterations in the psyche: depression, increased irritability, restlessness, impairment of memory, easy mental fatigue and many other symptoms. He has explained the phenomenon as originating

in the vasomotor center of the brain. A stimulus is sent to the splanchnic region, this entire region of the abdomen then contracting and a large amount of blood being forced into the peripheral vessels. As the result of such a displacement of blood there are feelings of faintness, palpitation, oppression, air-hunger and anxiety. Thus the subjective sensations have an objective explanation. The regular recurrence of vasomotor waves at intervals, day or night, is often remarkable. The patient's sleep is very much disturbed and a state of severe fatigue often ensues.

It is not surprising that a woman who experiences one of these vasomotor waves for the first time becomes much concerned. Her fear becomes directed usually to one of the vital organs involved, depending on which location the stimulus received is the strongest. One woman will complain of gastrointestinal sensations, of a "queer feeling in the epigastrium," "nausea," "gas," "bowel-spasm," or "a little convulsion of the bowel"; another will complain of "palpitation" and "shortness of breath"; still others of a "bursting fullness" in the head. Perhaps palpitation makes the patient "heart conscious" for the first time, and she immediately begins to worry about heart trouble. She goes to a doctor and complains of a rapid and irregular pulse, palpitation and fluttering; it keeps her awake at night. She is short of breath on exertion. She may not mention the other sensations of the vasomotor wave, her mind being too fixed on her heart. The vasomotor waves may even have subsided and left only the cardiac neurosis of the menopause. Many neuroses of similar origin supervene during this period. Perhaps the most unfortunate victims are those with whom sweating is the most prominent feature of the wave. These women will be seen in midsummer wearing woollen garments and even furs because they "chill so" after sweating. Several such patients say they have ceased to have any sensation of heat: all they complain of is "drenching perspiration followed by great chilliness," which occurs at regular intervals.

In a majority of the cases in which women suffer from these vasomotor disturbances a morning specimen of urine will reveal an excess of prolactin or anterior pituitary gonadotropic hormone; 60 c.c. of urine only are required. This may be injected directly after shaking with ether to get rid of the estrin. How-

ever, many more positive results are obtained by an alcohol precipitation method. The prolactin is precipitated with alcohol and the precipitate is injected into white rats twenty-one days old. These rats, with their control, a litter mate, are killed 100 hours after the first injection is given and the ovaries and uteri are observed grossly and weighed. The ovaries are then embedded in paraffin, and cut, stained and observed for evidence of follicle stimulation or luteinization. When the latter is present, we consider the hormone to be present in greater amount than when follicle stimulation only is observed. If a positive result is obtained with 3 c.c. of unconcentrated urine, 330 units of prolactin are present in a liter of the patient's urine. When the urine is concentrated five times by the alcohol concentration method, 66 units are present. It is not necessary to estimate the amount of prolactin exactly, although two or three dilutions give a better idea of the excess present. All that is necessary is to determine if prolactin is present in excess amounts. It is well to determine the value for estrin in a twenty-four hour specimen of urine about the same time as the morning specimen of prolactin is obtained and, if possible, to obtain a twenty-four hour specimen of urine weekly for the determination of estrin to see if any ovarian function is still present. In cases in which patients have had a fairly recent menstrual period the test for excess prolactin may be negative, for we observe them at a time in the cycle when estrin is present in sufficient amounts to suppress pituitary function. If several determinations of urinary prolactin are made, one will be sure to get a test positive for excess prolactin at some time during the monthly cycle. This will fairly well correspond to the period when estrin is lowest or absent, and it is during this period that the vasomotor disturbances are present.

In women suffering with vasomotor disturbances long after ovarian function has ceased, as evidenced by atrophy of the genitals and negative estrin tests, a test for excess prolactin should be positive if pituitary hyperfunction still exists. The test is all important in these cases as only those who show excess prolactin seems to respond to hormone therapy. It is our custom to repeat a negative test. It would seem quite probable that in the other cases, the nervous system has continued a vicious

habit of vasomotor waves and for these patients, psychotherapy and sedatives accomplish more.

In the past two years we have seen eighty-four women at the Clinic who complained of hot flashes or symptoms that were considered to be of functional origin and possibly related to the menopausal syndrome. Fifty-nine of these women were having hot flashes of from grades 2 to 4. With the exception of four women, all were more than forty years of age; the oldest was seventy-one. Of the four women less than forty, three had had their ovaries removed for tumors; one woman of

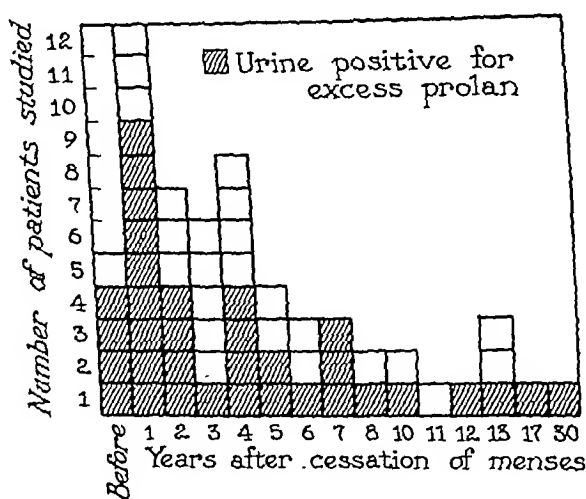


Fig. 52.—Results of tests for excess prolactin: Outlined squares show number of patients studied (59), shaded squares show number for whom the urine was positive for excess prolactin (34).

thirty-five years had had spontaneous cessation of periods at the age of twenty-eight. Of the women more than forty years of age, five were still having their menses. Of these fifty-nine women who were having severe, hot flashes, the urine of thirty-four (57.6 per cent) gave a positive test for excess prolactin (Fig. 52).

This study substantiates the findings of others that the majority of women with vasomotor disturbances sufficient to bring them to the physician belong to the second period of the climacteric, the period when the menses are ceasing, and this is the period when the greater number show excess prolactin.

Perhaps, had we used a method of extraction that would have precipitated more prolان, or tried to do a quantitative determination, we would have found a much larger number of women whose urine showed more than a normal amount. By the Aschheim-Zondek alcohol concentration method which we used, a positive test is evidence of the presence of at least 66+ units per liter. The normal amount would perhaps not exceed 16 units.

Österreicher found 50 per cent of his cases positive for 330 units, 60 per cent positive for from 110 to 80 units and 92 per cent positive for 55 units. The urine of ninety-six of 105 women, fifty to ninety-three years of age, reacted positively for excess prolان. Several examinations of the urine were made in some of these cases before a positive test was obtained. Österreicher was able to demonstrate luteinizing hormone in 8 per cent of his cases. Of 105 old women, seven showed it, and of five who had been castrated, two showed it, four and twelve years after gastration—typical yellow bodies next to ripe follicles. He found blood points in only one case, that of a woman who had cardiac decompensation. The urine in this case was concentrated ten times. The same patient half a year previously, before decompensation had taken place, had been negative on five-fold concentration of the urine.

The oldest woman in the group we studied came to the Clinic primarily because of dizziness and various sensations of pressure and tension in her head. These were taken to be arteriosclerotic manifestations. She stated that she had had hot flashes for thirty years since spontaneous menopause at the age of forty. A morning specimen of urine was obtained and was found to contain excess prolان. The cross section of an infantile rat's ovary (Fig. 53, *a*) shows the follicle stimulation we consider as an evidence of the presence of excess prolان. Another woman, fifty-eight years of age, the mother of eight children, came to the Clinic primarily because of nervousness, which she stated made her have palpitation, weakness, faintness and blackness before her eyes, cold chills and shaking spells. Such a train of functional symptoms had developed that her home physician and family had considered placing her in a hospital for nervous and mental diseases. Her periods had ceased ten years before, spontaneously. Her urine was

strongly positive for excess prolactin (Fig. 53, *b*) which proved that many of her symptoms could be explained on a physiologic basis.

Another woman, fifty-four years of age, reported at the Clinic in June, 1935. She had had her right ovary removed twenty-eight years before, elsewhere, because of a cyst. Her menses ceased at the age of forty-six. Following this she stated that she began having attacks of epigastric pain which sometimes came on at or immediately before, and at other

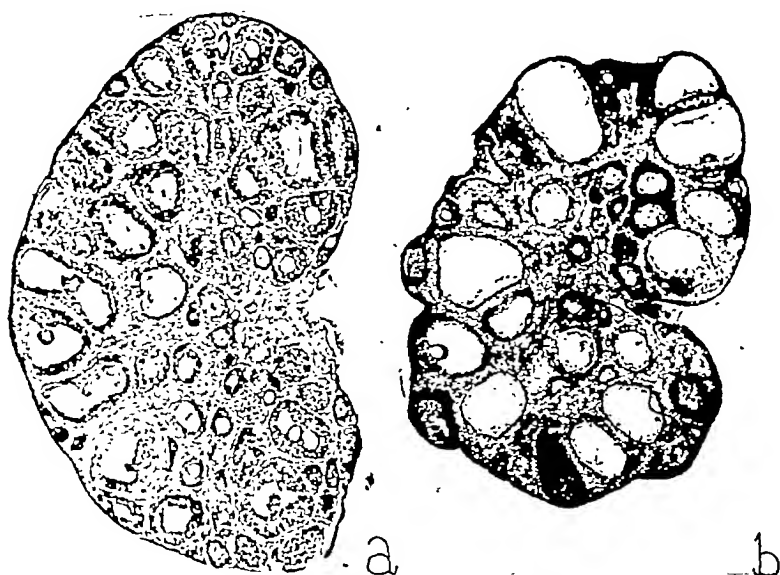


Fig. 53 —*a* and *b*, Cross sections of infantile rats' ovaries, showing follicle stimulation (case 1 and 2).

times an hour or more before, meals and also awakened her at night. This history was fairly clear for ulcer. On physical examination she was found to have a large ovarian cyst, and roentgenologic examination of her stomach revealed a small gastric ulcer near the lesser curvature, with hour-glass deformity. She was operated on June 12, 1935. A large cystic tumor was found lying between the folds of the left broad ligament. There was no evidence of a left ovary. On July 5, 1935, partial gastrectomy was performed for gastric ulcer, a posterior Polya type of anastomosis being made. The patient

returned to the Clinic February 5, 1936. She came chiefly because she had been told to return for reëxamination of her stomach condition. She stated that since the operation she had had attacks during which she suffered from dizziness, weakness, palpitation, a sense of warmth, nausea, vomiting and sweating, the entire attack lasting about five minutes and being associated with considerable nervousness. She said she had some epigastric pain during these attacks, which was

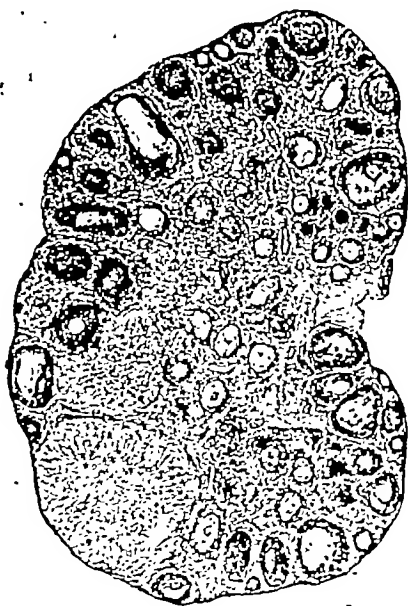


Fig. 54.—Marked excess of prolan as evidenced by corpora lutea in the ovary of an infantile rat (case 3).

situated over the site of the incision, but that this pain was not nearly as severe as before operation. At first she gave the impression that these attacks occurred after meals, and it was felt that she might be suffering from a widespread sympathetic reaction resulting from rapid dilatation of the jejunum. While she was under observation the attacks were timed and they were found not to occur particularly after eating; a note was then made that there were apparently other triggers. No clear history of ulcer could be elicited. The morning speci-



men of urine revealed a marked excess of prolactin, as corpora lutea were present in the ovaries of the experimental animals (Fig. 54). Before the report of the prolactin test was obtained the patient was given an injection of 2,000 International units of theelin-in-oil every other day for three times; she did not improve and was sent home, phenobarbital being prescribed for her. This medication has helped her some. After the report of the prolactin test it was evident that the three ampules of theelin were not sufficient to produce any amelioration of symptoms.

Twenty-seven of these eighty-four women in the climacteric came for bizarre complaints which had come on since the cessation of their menses but they were not complaining of hot flashes. Five of these women had excess prolactin in their urine. Estrogenic hormone was advised in these cases in similar dosage to that given to patients with hot flashes. All of these five women reported they were better.

Much has been written about the gain in weight that takes place after cessation of the menses. No doubt some unknown endocrine factor at work is partly responsible for this. Marinus has recently suggested that the obesity is due to a nervous hunger; they may become hungry faster owing to the faster emptying time of the stomach and increased peristalsis. This may be an effect of excess secretory function of the posterior lobe of the pituitary body. Women state that they have less trouble with constipation, and some even have frequent, loose stools during the climacteric period, probably, also, owing to increased activity of the posterior lobe. In some cases nails and hair grow more rapidly during this period, which suggests an increase in the secretory function of the cells producing the growth hormone. It would appear probable that there is some excess secretion of all the pituitary hormones during this period.

**Treatment.**—Treatment of the second period of the menopause is directed chiefly toward control of the distressing symptoms associated with ovarian failure, particularly vasomotor disturbances. These may have been present for several months before any menstrual periods are skipped. They seem to occur at two times in the cycle, about the midinterval and during the period itself, when they are often most disturbing.

It is known that these are the two times in the cycle when prolactin is present in greatest amounts in the urine; estrin is lowest during menstruation.

Before treatment is begun, a morning specimen of urine is tested for excess prolactin. The character of the vaginal smear is also studied. This has proved a valuable aid in therapy as it is possible to tell by vaginal smears, according to the method of Papanicolaou, when treatment has become effective. A subsidence of symptoms should come with the presence of the typical cornified or leukopenic smear in the vagina.

In the ordinary case treatment is begun with a daily injection of 1 c.c., 1,000 International units, of theelin-in-oil (Parke, Davis and Company). The patient is told that she will not notice much change in her symptoms for from six to ten days, which time is necessary to bring about a suppression of pituitary function. It is probable that there may be an ovarian hormone the lack of which may be directly responsible for the vasomotor disturbances. Marinus reported, at the recent session of the American Association for the Advancement of Science in St. Louis (January, 1936), that subcutaneous injections of a substance of the whole ovary would stop hot flashes immediately and the effect would last forty-eight hours. I have had no experience with this substance.

If the patient is much fatigued from loss of sleep as a result of the frequent occurrence of hot flashes and sweats at night, she is given  $1\frac{1}{2}$  to 3 grains (0.1 to 0.2 gm.) of amytal at bedtime after a warm relaxing bath. She is told to avoid heavy bed clothing and to sleep in a cool but not a cold room out of a draught. Administration of amytal is continued until the theelin begins to produce its effect; it is then easily discontinued.

In cases in which the gastro-intestinal symptoms are prominent, small doses of phenobarbital, for example  $\frac{1}{2}$  grain (0.03 gm.) three times a day after meals, may need to be given for a time with the theelin. A smooth, easily digested diet, and when nausea is present frequent feedings, add much to the patient's comfort. Coffee, tobacco and alcohol should be avoided; they may give a temporary sense of comfort, but the vasomotor mechanism is made constantly more unstable by any undue stimulation.

After twelve to fourteen injections of 1,000 rat units of theelin-in-oil have been given, it is often possible to reduce the daily dose or to skip a day. Whenever the amount of theelin is reduced, reduction should be very gradual so as not to re-stimulate the pituitary. It is best to carry the patient for several weeks on at least three injections a week before cutting down further, and then, if possible, to switch over to an oral preparation, the one most familiar to me being progynon (Schering Corp.). Two tablets (45 rat units each) three times a day, before meals, are usually necessary to control vasomotor disturbances. The symptoms of many women not controlled with the 1,000 units daily of theelin-in-oil are easily controlled with 2,000 International units. After they have had this for twelve days and their symptoms have subsided, the dose is very gradually reduced.

For women who are still menstruating but who are having disagreeable vasomotor disturbances this treatment is kept up regularly also. It has not seemed to make much difference about the regularity of menses. The dose of theelin necessary to control hot flashes is probably not sufficient to postpone menstruation. Larger doses will do this at times, and when large doses are necessary for young women to control disagreeable molimina, it is always best to stop the administration of theelin four days prior to the regular time of onset of the period. Many women during the menopause need to continue taking theelin for a year or two years. They may cease having symptoms and go without treatment for a time, when treatment will have to be resumed and theelin again will be required in daily doses for a time. Patients are switched over to progynon by mouth as soon as it is felt it will carry them.

Certain women suffer during this second period rather long-continued phases of depression; as they express it, they usually feel very tired and depressed, are fearful and tend to worry about trifles. The usual accustomed work looks big to them and they dread to undertake it; they even hate to make any effort to be social. they are irritable and sensitive, emotionally unstable. cry easily and occasionally have nervous "spells" when they feel as if they were losing their minds; they "can't think." or they "shake all over and have to go to bed." Attacks of depression may alternate with periods of feeling very elated

and stimulated. They are as conscious of this false sense of stimulation as they are of depression. These states are usually present while the vasomotor disturbances are present. As has been noted before, however, the psychic states may impress the patient more than the vasomotor phenomena and be more emphasized. Theelin therapy improves this mental state very much. Coincidental with treatment sufficient to produce the vaginal reaction, a sense of well-being and of self-confidence and stability returns.

Certain skin manifestations are prone to occur during the menopause which also appear to be helped by theelin therapy: urticaria, angioneurotic edema and atopic eczema. The urticarias are apparently directly related to estrin deficiency and not to excess pituitary secretion, as they occur in young women with ovarian deficiency and amenorrhea when not even normal amounts of prolan can be detected in the urine.

Asthmatic attacks and epileptiform seizures beginning at this age period may also be related to an endocrine imbalance. Not enough endocrine studies have as yet been made in these cases to arrive at any conclusion as to what hormone deficiency is responsible. There are many bizarre symptoms which women complain of during this period that are at times associated and at times unassociated with vasomotor waves, such as continuous parietal or occipital headaches, pressure in the head, sinking spells, disturbances of equilibrium and aching in the lower part of the back and in the thighs. If no organic cause is found to account for these, we at the Clinic consider theelin therapy, provided the test for excess urinary prolan is positive.

Patients who have hypertension seem to need larger doses of theelin to control the vasomotor symptoms; on the other hand, theelin seems in these cases to have a beneficial effect on the blood pressure. Hypertension frequently begins to develop in this age period, as has been noted by Schaeffer, and theelin helps to reduce it.

Occasionally one finds women who have continued to have these vasomotor disturbances for an unusually long time. Urinary prolan is not in excess; perhaps not even normal amounts can be detected. Metabolic rates are lower than normal. Giving these women desiccated thyroid gland has made

them feel better, and sleep and eat better, and after a time the hot flashes have ceased. It would appear as if the pituitary had ceased its overfunctioning and was reacting with less than normal function, reducing metabolism and inducing fatigue, and as if the nervous system of the fatigued patient had continued to respond to stimuli keeping up the vasomotor waves.

Much advice in a general way is given these women in the climacteric. They are advised to spend a great deal of time in the open air, to take regular exercise and to keep to their usual routine of work or business. The woman who has time to observe the exact time of each flash, so that she can tell you just how many she had during the day, must be warned that she is allowing the impressions made on her conscious mind to sink too deeply, making nerve paths which may become too fixed and making the habit persist after the glandular stimulation has ceased. It is advisable, therefore, to let the process go on as unconsciously as possible. The woman, then, who is forced to keep busy and to forget herself is the more fortunate one; however, she must find more time for frequent periods of relaxation and rest to compensate for her disturbed rest at night or complaints related to chronic fatigue will develop. Currier once wrote, "All that tends to develop and strengthen the physical part of woman, to render her insensitive to the ordinary ills of life, to make her forgetful of self, is favorable to a normal menopause."

### PERIOD 3

Period 3 is the period of atrophic change in the accessory organs which is brought about by a continued lack of ovarian estrogenic hormone. This hormone is found to be absent in the blood and urine with the usual test methods. Conditions such as pruritus vulvæ, kraurosis vulvæ and atrophic vaginitis may be present. Hot flashes may have subsided, depending on the subsidence of anterior pituitary function, with overproduction of gonadotropic hormone. The blood and urine may still show an excess of this hormone.

**Symptoms.**—To some women this period brings more actual distress and discomfort than any preceding period. Their symptoms are related to atrophic changes about the vulva or

the vagina, or both. The complaint which brings the greatest number of patients to the physician in the early stage of atrophy is itching. Burning is associated if friction and a resulting inflammation of the skin have ensued. Itching is extremely likely to begin in the fourchet or in the skin of the perineum, and for some time it may remain localized in these regions, or it may spread and involve the labia and clitoris and extend posteriorly about the anus. The inflammatory process, if present at all, is most marked at the beginning. The entire vulva may be swollen, the folds standing out prominently. The skin appears stretched, glistening and pale. The shrivelling-up process then begins to be evident. The labia minora becomes smaller, the vaginal orifice becomes greatly narrowed, and the mucous membrane appears very pale and even white; at times it may appear very white and thick and almost leathery. To this shrivelling-up process has been given the name "kraurosis vulvæ." These changes may all be considered entirely physiological, the result of a loss of ovarian function.

**Treatment.**—During the third period of the climacteric, treatment is related to the symptoms associated with atrophy of the genitalia. The itching associated with the onset of the atrophy often responds to injections of theelin-in-oil. Usually, to influence this condition of the skin and mucous membrane, it is necessary to begin with larger doses of theelin. Two thousand International units are given daily and are continued until the full effect of treatment is noted in the vaginal smear. This usually requires ten to twelve injections, and injections must usually be continued three times a week for from four to six weeks. It is frequently possible to see grossly a change in the mucous membrane of the vagina and vulva. The mucous membrane changes from white or pale-pink to bluish-red, and from a dry to a moist texture, and the symptoms subside.

The first advice given the patient should be in the form of a warning regarding scratching or rubbing the parts: soap should not be used on them. Often, to allay a paroxysm of itching, soda water (about 5 per cent sodium bicarbonate) is applied as hot as it can be borne by bathing the parts or by sponging and then not drying the skin. The cooling effect of evaporation of the fluid causes vasoconstriction. Fantus has called attention to this. If burning and inflammation are

present, packs soaked in an 8 per cent solution of aluminum subacetate, 1:16 parts of water, is helpful. Oily lotions, such as olive oil and lime water or Schamberg's lotion,<sup>1</sup> have seemed to relieve many patients. The lotion is applied nightly, and oftener if necessary.

Leukoplakic areas may develop on this chronic atrophic process; these are discrete plaques involving the inner surfaces of the labia majora and labia minora, fourchet or around the clitoris, and they may cause the most intense itching. They are grayish, and there is definite thickening of the skin or mucous membrane; fissures or ulcerations may occur about these areas. When these leukoplakia areas are present, it would seem unwise to resort to theelin therapy as they are precancerous lesions. Surgery, either excision or vulvectomy, is the only safe treatment. Adair and Davis have recently emphasized this.

A patient may complain of burning and of a feeling of fullness in the vagina. This may or may not be associated with sufficient discharge to make her conscious of it. On inspection the vaginal mucous membrane appears thin, glistening and reddened; one may see the vagina peppered with red spots, 1 or 2 mm. in diameter, patchy areas of redness, or it may be diffusely reddened. The fornices may be closed by adhesions of the cervical lips to the vaginal walls. Contractures of the vagina may be present. Small punctate ulcerations of the mucous membrane may be seen in the upper part of the vagina. When considerable redness is present, evidence of a superimposed acute inflammation, the discharge may be quite purulent; otherwise the discharge is usually milky. Some gross blood may be present in the discharge or the discharge may appear pinkish. The discharge is not mucoid unless an old chronic cervicitis is also present. This atrophic type of vaginitis also responds very well to theelin therapy. When vaginitis alone is present and there are no vulvar symptoms, 1,000 International units of theelin are given daily until the effect of treatment is noted in the vaginal smear. It is well to give some mild local treatment during the first week to help clear up the coexisting infection. *Trichomonas* are often found

<sup>1</sup>Menthol 0.6; phenol 4.0; oil olive 120.0; liq. calcis 120.0, and pv. zinc oxide 200.

in a hanging drop of the fresh smear. Bacteria are plentiful. Painting all of the vaginal and cervical mucous membrane with a watery solution of gentian violet 1:500 will help greatly to clear up the infection present. Keeping the vagina packed with kaolin (Merck's) to absorb the secretions facilitates this and this drying out process is often sufficient to rid the vagina of the *Trichomonas*. It is surprising how quickly the vaginitis and the corresponding symptoms will clear up. The injections of theelin should be kept up from four to six weeks, three times a week after the first ten to twelve days according to the procedure outlined by Davis. Treatment can then be discontinued and the patient may have no further trouble. If the symptoms recur, another course of treatments can be given. After the vaginitis has cleared up, it is easier to tell whether any chronic cervicitis is present. A light cautery will take care of this.

It is wise to tell women suffering from this atrophic or senile type of vaginitis that the condition may recur and that another course of treatment may be necessary. It is well to warn them also that when any blood is present in the discharge, a physician should be consulted so that a decision can be made as to where the blood is coming from.

Thus each of the three periods of the menopause has its own problems and specific therapy. During the first period the failure of the ovaries to produce normal corpora lutea brings about an increase in the amount and duration of the menstrual flow. If curettage reveals only the characteristic endometrial picture, luteal hormone will frequently control the bleeding. If it does not, removal of the uterus or a menopause dose of radium or roentgen rays is in order. During the second period, that of the vasomotor disturbances, when the pituitary is hyperfunctioning as evidenced by the excess prolactin found in the urine, the estrogenic hormone of the ovaries given in sufficient dosage will suppress the pituitary function and thereby allay the patient's symptoms. During the third period, when atrophy of the external genitals consequent to an absence of ovarian secretions is marked enough to produce symptoms of itching and inflammation, estrogenic hormone will restore the mucous membrane to a condition corresponding to the follicular phase of the menstrual cycle, which is of definite therapeutic benefit to the patient.



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**SYMPOSIUM ON CARDIOVASCULAR DISEASES**

The following clinics are included in this Symposium:

E. J. G. Beardsley: **SIMPLICITY IN THE DIAGNOSIS OF CARDIOVASCULAR DISEASES.**

Charles C. Wolferth: **THE DIAGNOSIS AND TREATMENT OF ACUTE CORONARY OCCLUSION.**

Henry K. Mohler: **MISSED CARDIAC DIAGNOSIS.**

John H. Stokes and Leonard E. Anderson: **THE DIAGNOSIS AND TREATMENT OF SYPHILITIC AORTITIS.**

Joseph B. Vander Veer: **THE DIAGNOSIS AND TREATMENT OF ABNORMAL CARDIAC RATES AND RHYTHMS.**

Edward Weiss: **SYMPTOMS OF HEART FAILURE IN HYPERTENSION.**

Mary Hoskins Easby: **THE EARLY RECOGNITION OF CARDIAC INSUFFICIENCY IN THE PRESENCE OF PREGNANCY.**

Charles L. Brown: **USE OF DRUGS IN CARDIOVASCULAR DISEASE.**

George C. Griffith: **DIET IN THE TREATMENT OF HEART DISEASE.**



## CLINIC OF DR. E. J. G. BEARDSLEY

JEFFERSON MEDICAL COLLEGE

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### SIMPLICITY IN THE DIAGNOSIS OF CARDIOVASCULAR DISEASES

**Introduction.**—The inauguration of still another college session in Jefferson's historic clinic serves to emphasize the truth of the radio slogan, "Time Marches On."

Any physician who has been actively connected with a clinical branch of a medical school's curriculum for over thirty years has had both time and opportunity to develop firm convictions regarding how he may prove most helpful to students, undergraduate or graduate.

In any clinic, well advanced in its second century of usefulness, almost exclusively devoted to the education of undergraduate students and to the interests of the sick poor, there are bound to exist inspiring traditions and time-approved clinical methods of investigation and study.

One tradition we have at Jefferson, ancient as the school's origin, concerns the firm belief of the founders that the status of a nation's medical profession can best be judged by the character, education, training and skill of the general practitioner of medicine.

We believe today, as the founders of the Jefferson Medical College believed in the early portion of the nineteenth century, that our school can serve no higher or more useful purpose than to provide a sound general medical education, with proper emphasis upon the essential foundations for a vital and comprehensive medical philosophy and with even greater insistence upon intensive clinical instruction for those who will, by these measures, be properly prepared to become general practitioners of medicine.

We are convinced, by observation and long experience, that a well-educated and conscientiously-trained general prac-

itioner of medicine of the right type is the most generally useful, although, unfortunately, not the most usually appreciated physician in the world today.

Whether a physician continues throughout his professional life as a general practitioner or whether he, later, enters a specialty, the discipline and training in general practice, providing it has been of the progressive, enlightening and inspiring variety, cannot but have made it possible for him to have been particularly useful to his patients.

It is exceptional to observe a specialist who has not enjoyed the broadening experience of general practice, whose professional judgment is as sound as one who has been aided by such a helpful experience.

The founders of our school believed that superior qualities of character, combined with such helpful essentials as natural aptitude for the duties and responsibilities of the medical profession, the possession of "the saving grace of common sense," intellectual honesty and, not least in importance, the possession by the candidate of a sincere and altruistic interest in helping those in trouble comprise far more important qualifications for an individual entering and remaining in the medical profession than the possession by the candidate of brilliance of intellect, superior scholastic marks and exaggerated self-interest.

It is true that the founders lived in a different century than the present but who can deny that the sick, in any century, need the services of kind and skilled physicians of integrity and honor whose chief object is to serve, as best they may, the interests of their patients.

We believe today, as the founders of this school believed long ago, that the profession of medicine is an art that is firmly based upon a knowledge of science.

We are convinced that medicine can never become an exact science, if for no other reason than because the individual patient is unique.

The arrangement and potentialities of the many chromosomes that comprise each embryo produces an individual unlike any individual who ever lived and, likewise, unlike any who now live or will live in the future.

Each patient's reaction to life, to environment, to health,

to disease and to drugs and other therapy are all, far beyond our present knowledge and understanding, uniquely individualistic.

It is, fortunately, true that medicine has a sound foundation in science, its methods and procedures are improved and greatly advanced by science and by the improvements in scientific methods but the everyday practice of medicine will ever be, as in the near and remote past, an empirical art.

The more rounded a student's education before entering the medical school the more fortunate both the student and his future patients unless it be, as sometimes happens, that a medical neophyte mistakenly magnifies the importance of book knowledge and fails to interest himself in human beings whom he, later, wishes both to understand and to serve.

It is traditional, unfortunately, that the word "study" usually indicates to a medical student, undergraduate or graduate, intimate contact with the contents of a book but, if the truth was known and fully appreciated, it would be to any student's advantage if he could spend more time in intimately studying and obtaining an extensive first-hand knowledge of normal, average, well people.

It is to be remembered that, although much time has elapsed since Rousseau, in 1754, expressed the opinion that "the most useful and least advanced of human knowledge seems to me to be of man himself" conditions regarding an intimate and comprehensive knowledge of human nature by members of the medical profession have changed all too little.

It is a serious reflection upon our lack of vision as teachers in medical schools that charlatans and other pseudomedical cultists frequently exhibit evidence of far more profound understanding of human nature, in its infinite varieties, than do many classically educated and so-termed "scientifically" trained physicians.

Certain physicians of limited vision and unworthy of the best traditions of their profession are inclined to view their patients as pathologic material provided by nature for the economic improvement of the doctor and not as unfortunate human beings who are in trouble.

It is surprising that, through all the centuries, so few medical curricula have emphasized the importance to the medical

student and physician of the future of an intimate knowledge and perfect understanding of the psychology of men, women and children in health as well as in their periods of illness.

The medical student, undergraduate or graduate, who desires to prove most helpful to his patients will do well to remember that the patient, in the majority of instances, is much more difficult to understand than is the disease process that affects him.

One cannot, I think, emphasize too vigorously the wisdom, even the practical necessity, for early acquiring and continuing to acquire throughout life, an intimate knowledge and understanding of varying types of individuals, living under different conditions of environment, in health, as an all important training for the comprehension and helpful understanding of similar individuals when they become ill.

The more intimate and extensive one's understanding of human nature the easier it becomes to understand the psyche and the peculiarities and idiosyncrasies of those individuals who are ill.

Medical curricula, unfortunately, are not influenced by the experiences of recent graduates who are in a position to fully realize the weaknesses and deficiencies of the plan of education and training that was provided them. Such graduates could, undoubtedly, give helpful suggestions for improvement in the courses of study and training but medical curricula are, as a rule, traditional relics from the remote past that change little with the years and are influenced only remotely by the experience, in practice, of the school's graduates.

Before a medical student arrives at his "clinical years" he is fortunate who has acquired, by heredity, by environmental contacts and by general observations, a philosophical point of view that can be, if occasion arises, altered as he increases his experience and grows in wisdom.

The observing student will soon learn that, although political orators may declare with winged words that men are born free and equal, no naturalist or physician believes this to be true of either physical, emotional or intellectual characteristics.

That wise physician and sound medical philosopher, Oliver Wendell Holmes, expressed an incontrovertible truth when he

stated that, "man is an omnibus in which all his ancestors ride."

It is an amazing evidence of the intellectual myopia that sometimes afflicts medical teachers and the medical profession's leaders that, through the centuries, so relatively little attention has been directed to the paramount influence of hereditary factors as vitally influencing health, happiness, and disease.

Hereditary influences are the most important single factor influencing a life in health and it is, probably, a far more important determinant than we, at present, understand in disease prevention and production.

Any one physician's active professional life permits him to see and study but two or, possibly, three generations of individuals, sick and well, and by the time he has become thoroughly acquainted with the ancestral characteristics, susceptibilities, resistance and peculiarities of his patients, Charon's Ferry awaits him.

It is difficult, if not impossible, to efficiently transmit to others the patiently and, all too slowly, acquired information regarding observed hereditary factors and influences that have been obtained through a professional lifetime.

Any physician who, from his early years in clinical experience, resolved to faithfully study and systematically record the observed influence of hereditary factors influencing health and disease would, in all probability, be able to produce an important and influential medical classic.

When the medical profession increases in wisdom, as much time and thought will be devoted to the influence of heredity and environment upon the sick public as is now spent in vainly seeking therapeutic panaceas for chronic degenerative diseases.

Another curious and unfortunate anomaly in undergraduate medical instruction is the paucity of, officially provided, opportunity and encouragement for systematically investigating normal individuals under varying conditions of rest and exercise and under circumstances of emotional and physical stress.

Each medical student would do well to take advantage of every opportunity for making a painstaking and thorough survey of both the physical and psychic state of normal individuals.

Students, both undergraduate and graduate and, unfortunately, practicing physicians as well, are all too likely to consider a thorough survey of a normal individual an uninteresting and profitless procedure.

Such an examination, systematically and thoroughly performed, is, in reality, a most helpful, valuable and educational discipline.

There exists a prevalent impression, both in lay and medical circles, that the profession of medicine can be greatly improved and rendered more "scientific" if physicians limit their professional interests to one organ or to a closely related group of organs. This attitude of mind has resulted in a particularly unfortunate psychologic aspect of modern medicine.

When well educated and thoroughly trained physicians begin to doubt their ability to properly diagnose and treat the common disorders of the most vital organs of the body it is a matter for deep concern.

Since the World War one has had occasion to note the gradual acquisition by many excellent and even superior general practitioners of an entirely unwarranted and unmerited sense of professional inferiority and inadequacy in connection with their ability to worthily serve the best interests of their patients.

Contrasting unfavorably with this unhappy, soul-searching mental attitude of the earnest, conscientious family physician there have been, at times, opportunities for observing an equally unfortunate and unwarranted assumption of professional superiority by inexperienced physicians who possessed limited professional vision and whose assumed superiority was, all too often, based solely upon the restriction of the individual's professional interests to a single organ.

The lay public is not in a position to wisely judge medical matters and one finds that public opinion mistakingly supports the view that a long list of "specialists" are a necessity in modern medicine.

If, on the other hand, one obtained the carefully weighed opinion of the majority of experienced physicians upon this subject it would be learned that, in their judgment, the most generally helpful physician is the well educated, carefully trained, conscientious general practitioner.



There is no activity in medicine in which a well prepared physician can be more generally useful than in general practice nor is there equal opportunity in any other medical field in which there is less spirited competition in performing, each day, superior medical work.

The excellent general practitioner, properly educated and thoroughly trained, is, in reality, a superior and greatly needed specialist in a very broad and inclusive professional field.

When the intelligent lay public awakens to a sense of relative values and becomes willing to properly support in appreciation, and in suitable remuneration, the best type of family physician the medical profession will be in a much more equable economic situation and this will be in the interest of all that is best in medicine.

If a physician desires to become a skilled specialist there is no better preparation than is to be found in the general practice of medicine. The illuminating experience to be gained and profited by as a general practitioner loses nothing of its intrinsic value when added to the training and technical experience of the especially trained worker in a more limited field.

There are surgeons who are excellent operators whose professional judgment would have been materially improved by the educational advantages of a period of experience in general practice and the physician who enters a specialty without experience in the common disorders of everyday medicine, must overcome a serious handicap and, take precautions against acquiring too limited a view of his specialty and, even more important, too limited a view of the ills of his patients.

We believe that for centuries past physicians have had the greatest opportunities for service to their fellowmen. We are convinced that, taking it all in all, physicians have rendered and do render good and efficient services but it is well for all in the medical profession to remind themselves occasionally that they exist, solely and entirely, for the services they are able to render others.

The application of the Golden Rule in our relationship with our patients is a wholesome deterrent for unfair practices.

**The Clinical Demonstration.**—It is pleasant to begin a series of demonstrations of patients who will illustrate the common or garden varieties of cardiovascular disorders. For

the information of newcomers in the class and for the enlightenment of our ever welcome professional visitors it is well to make the statement that this clinic represents conservative, classical methods of investigation and study.

In this arena, and on many occasions, the eloquent clinical teacher, J. Chalmers Da Costa, stated, with the facility for striking and easily remembered phrases that was so characteristically and inimitably his own, "an intuitive diagnosis is, all too frequently, a rapid and sure method of arriving at a wrong conclusion."

Every clinician who has yielded to the temptation of making a diagnosis without the possession of complete and reliable data can vouch for the truth of that great surgical teacher's statement.

We believe, as Dr. Da Costa and all other good clinicians have believed, that correct diagnoses depend upon a carefully ascertained and properly recorded history, a systematically conducted and painstakingly thorough physical examination, an interested survey of the patient's psychical state, plus the often invaluable confirmatory help afforded by carefully conducted laboratory investigations.

It is well to warn undergraduates of the, often entertained, false impression that clinical medicine ever has been learned, or ever can be learned, in a lecture hall or in a clinical amphitheater.

At best we can hope that you who sit upon the benches can obtain helpful hints as to clinical procedures and methods that you will, individually, carry out, gain familiarity with technical terms and expressions and become acquainted, even from a distance, with the symptomatology and physical signs illustrative of disease.

You will perfect your methods of history taking and of performing physical examinations in the small sections of the class assigned to the dispensaries and wards.

It is well to remember, however, that it will take each of you a professional lifetime to perfect your knowledge along those important lines. A selected number of your group will assist at each clinic and, although you will not, at first, enjoy or appreciate this privilege you will learn by experience that appearing in public where you are to feel yourself "the ob-

served of all observers" is an excellent and invaluable discipline to rid you of a feeling of self-consciousness.

A physician, young or old, who is self-conscious and diffident is greatly handicapped in his professional work as well as in his social relations. Those students who are most reluctant to appear in the clinic as student associates will find that this, at first, unpleasant discipline is most helpful for their professional development. We are to be students together for, it is to be remembered, that a physician continues to learn all his life and when he can no longer increase his knowledge he has, as a rule, outlived his professional usefulness.

Before the first patient enters the arena it is well for us to enumerate the essentials for a correct diagnosis.

1. A carefully ascertained history, past and more recent.
2. A systematic and thorough physical examination.
3. The necessary laboratory investigations.

**Case I.**—The first patient we are to study is this genial, smiling, E. H., age thirty-two, white, American of German parentage. He comes before us this morning, not as a sick man, but because he is aware that he possesses what is usually termed, "an interesting heart."

The pertinent details concerning the patient's medical history can be briefly reviewed.

The patient's father died at age thirty-eight of complications incident to, or sequels of, attacks of acute rheumatic fever, namely, organic valvular heart disease. The patient's mother is living and in fair health at seventy-two years of age.

E. H. has no memory of any bed-confining illness until he was twelve years of age when he suffered from an acute febrile ailment that persisted for two months.

The patient states that the family physician termed the disease "rheumatism" although the present memory of the symptoms is confined to repeated attacks of epistaxis, the presence of abdominal aches and pains, much sweating and the presence of headache.

It is only when the patient is carefully questioned that he then remembers that his joints, especially the knees, ankles, shoulders and elbows, were painful and swollen and that he had marked difficulty in moving about in the bed. He remem-

bers, too, that his joints were wrapped in "red" flannel that had been saturated with a liniment possessing the odor of wintergreen.

He recollects, when questioned, that the family physician frequently examined his heart with a stethoscope during this illness and that he was repeatedly warned to take precautions against the tendency to overexercise.

At sixteen years of age, four years after the first attack of rheumatism and without, as far as the patient can remember, any particular exciting cause he was unfortunate enough to have a reoccurrence of the same disorder.

This illness was ushered in by the return of his periods of nosebleeding, much headache and fever and general body aches, accompanied by periods of profuse perspiration but there is no remembrance of joint pains.

The seizure at sixteen years of age is designated by the patient as a "short" attack, lasting but two weeks, as far as bed confinement was concerned, but there is a remembrance of great prostration following the febrile period and prolonged convalescence during which the doctor again warned the patient and his mother of the need for care because of the presence of a heart lesion. The physician at this time advised the patient to plan his life in order to avoid physical overstrain and thus it was that, at an early age, he deliberately selected music as a career.

The third attack of "rheumatism" occurred at age twenty-five, that is twelve years after the first seizure and nine after the second.

This illness at twenty-five years of age was very severe as can be concluded by the period of hospitalization for six months.

During this period the symptoms were frankly arthritic.

The patient remembers the illness all too vividly.

The knees, ankles, wrists and elbows were red, swollen and painful and much attention was devoted to the cardiac region by the attending physician.

Following this third attack of acute rheumatic fever the patient and his mother changed their residence and the son came under our observation and care.

We felt that it would do no harm to have the badly infected tonsils removed and this, in the patient's opinion, has resulted in an improvement in the general health by causing the throat to be less susceptible to infections.

Before us we have a patient thirty-two years of age who has had the misfortune to be afflicted with 3 attacks of rheumatic fever but, fortunately for him, with the exception of those 3 periods of illness the patient has enjoyed what he terms, "moderately good health."

He informs us that as long as he takes matters easily, does not exert himself too much and does not take too much food he continues to feel well.

He has learned by experience two particular hazards.

He cannot, without marked discomfort, use alcoholic beverages and, similarly, he cannot become emotionally disturbed without being made ill by the experience.

The patient states with emphasis that a difference of opinion with anyone upsets his circulation even more than does unusual physical effort. Having heard the medical history there is now an opportunity of examining the man.

We note that the pupils are equal and react normally. The teeth seem free from evidences of gross pathology and the tonsils have been thoroughly removed. There is but one method of making a satisfactory heart and lung examination and this involves the complete removal of the patient's clothing above the waist.

Suitable loose chest covering must be provided both for the protection of the patient from cold and that the patient may feel perfectly comfortable in mind during the examination but, it is to be remembered, that such chest covering should be so arranged that the areas under examination may be completely revealed.

The most difficult feature of the usual chest examination has to do with the removal of the body covering.

Complete and thorough examinations prevent serious mistakes and are, in effect, an efficient therapeutic measure.

As we now glance at the patient he, at first, appears a well-conditioned athlete. His color is excellent, there is no evidence of cyanosis, he is well nourished and appears free from distress.

When we come to study the man more carefully, however, we note that the flesh is flabby and the patient frankly informs us that he finds it most difficult to restrain his appetite to the quantity of food that his ability to exercise requires.

Those near the patient may notice that there is an unusual and abnormal pulsation in the arteries of the neck and, in addition, the veins of this region are prominent from abnormal distention.

It is well to remember that the palpation of an artery invariably reveals a definite pulse while a vein, no matter how large or distended, can never be felt to pulsate.

Those observers who are quite near the patient may readily note that there is a synchronous nodding of the head with each arterial pulsation in the neck. We can safely exclude in this patient's case, the effect of emotional disturbance upon his heart and vessels because he is a veteran of many appearances in this arena and, for the additional reason that, as a musician, he frequently appears before much larger and more critical audiences without pulse disturbance.

It is well to remember that there is but one method of becoming an expert physical diagnostician and this method consists in thoughtfully and painstakingly examining enough human subjects to perfectly familiarize oneself with all variations of human bodies, in health and in disease.

We will now have a student sit before the seated patient and ask him to determine the exact site of the cardiac apex.

This determination is, in my judgment, the most important single feature of any cardiovascular examination.

The student is surprised to note that, in spite of a chest well padded with fat, he is able to both see and easily palpate the apex beat of the heart in the sixth intercostal space at a point not far removed from the anterior axillary line.

The next student is asked to observe the precordial pulsations and to palpate the left border of the heart.

The student remarks that he does not think it probable that the left border of the heart can be felt in such a well nourished subject.

This is, unfortunately, a false impression, not limited to undergraduates. When the student attempts to palpate the border he finds that it can easily be accomplished. The

left border is found displaced well to the left of its normal position.

The next student will, by percussion, exclude the possibility of the heart being displaced by a collection of fluid or air in the right pleural space. Normal resonance is found over the right lung and this tends to exclude both the presence of fluid and of an excess of air, namely, a pneumothorax.

The student who located the apex beat in its displaced position is interested to learn the cause of a palpatory thrill that he felt over the cardiac apex. A vascular thrill has been well described as a palpatory murmur and a vascular murmur may well be considered an auscultatory thrill.

Each thrill and murmur is due to vibrations induced by blood currents but one learns by experience that certain murmurs do not produce perceptible palpable thrills and that certain vascular thrills do not cause demonstrable murmurs.

We will have the student who noted the thrill locate it again and inform us whether its appearance is synchronous with the apex beat of the heart or whether it is felt after the apex beat.

The student states that the thrill at the apex can be definitely felt prior to the apex beat and this indicates that the thrill occurs in the diastolic phase of the ventricles' activity.

A thrill, in this period of ventricular activity, felt at the apex usually indicates an obstruction at the mitral orifice.

We will now have the second examiner palpate the chest area over the base of the heart and the area superior to and between the clavicles.

At the base of the heart and above the clavicles a marked thrill can be felt. We find that the basal thrill occurs with ventricular systole and this is easily estimated by noting that the thrill is synchronous with the carotid pulsation that is so markedly evident.

The student whose hand has been resting over the body of the heart states that there is an additional thrill in this area, not occurring with the carotid pulse.

This thrill is much more evident than the thrill that is palpated at the cardiac apex.

It is obvious that in this patient's heart there are present abnormalities of blood flow that it is necessary for us to study and understand.

Over the apex there is a late diastolic thrill, due to left auricular contraction and we know that, in this area, such a thrill usually indicates an obstruction of the mitral orifice.

The systolic thrill at the base is, obviously, due to an obstructive lesion at the aortic valves for it is easy to palpate a similar systolic thrill in the neck arteries above the obstruction.

The long drawn out diastolic thrill felt over the precordium is due to a regurgitant flow of blood through the aortic valve as the blood abnormally returns from the aorta through an incompetent valve.

It is, in my opinion, most helpful for the examiner to be able to decide from the medical history, from inspection and skilled palpation alone what the probable nature of the cardiac lesion may be before he auscultates the heart. In the examination of this particular patient so exaggerated are the palpatory signs, that one can be confident of the nature of the lesions without the aid of auscultation.

We will now have an examiner listen to the various valve areas and tell us of the auscultatory evidence.

The student describes a loud and long murmur, occurring in ventricular systole at the apex of the heart.

Such a murmur is to be expected in so large a heart even if the valve leaflets were unaffected.

No orifice so stretched by hypertrophy of the left ventricle could be controlled by the normal valves.

The student is disappointed to note that the time of the murmur is not synchronous with the late diastolic thrill that he can feel so easily at the apex.

The student must learn, as every clinician is forced to learn by experience, that one must not be content to listen alone to a very small area about the cardiac apex but he must listen all about the apex of the heart and, especially, above the apex if he is to perfectly interpret the timing of mitral valve orifice murmurs.

The student has now located an area nearly 2 inches above the apex of the heart where it is easy to be sure that one hears two distinct murmurs. One occurs in the period of ventricular systole and one in the period of auricular systole, namely, occurs late in ventricular diastole.

It is interesting to note that the systolic (regurgitant)



murmur produces no palpatory thrill but the obstructive lesion at the mitral valve orifice causes a distinct late diastolic thrill.

When one listens at the aortic cartilage a loud, harsh and prolonged rasping murmur is heard and this sound is transmitted into the vessels of the neck. If one, however, listens to the area over the fourth, left, intercostal space close to the sternum one hears both a long and harsh systolic murmur that is most clearly audible at the aortic cartilage and an equally long but much softer murmur during the entire stage of ventricular diastole.

The murmur heard during ventricular diastole over the body of the heart is so much softer in quality of sound that many students find such a murmur inaudible until their attention is especially directed to the so-termed "silent phase" of diastolic relaxation.

To have the patient exhale and then, for a few seconds, stop breathing will, by exclusion of breath sounds, cause the heart murmurs to be much more evident.

This is a practice that can, with advantage, be adapted by all who auscultate the chest.

Any simple procedure that facilitates and makes easier the physical diagnosis of everyday medicine is worthy of adoption.

The question must arise as to the likelihood of the two diastolic murmurs, heard so nearly together on the chest wall, being caused by the same or different etiologic factors.

Here there is a great advantage in being familiar with the natural history and progress of rheumatic endocarditis.

It is unusual for rheumatic disease to attack other than the mitral valve in the first attack of acute rheumatic fever.

Aortic valvulitis is, as a rule, a complication or sequel of the second or of still later attacks of this devastating disease.

We can be almost certain that the mitral valve was involved long before the aortic valve and that we are now dealing, in this particular patient, with extensive pathologic changes in both the mitral and aortic valves.

Fortunately it is relatively rare in rheumatic hearts to have the pulmonary and tricuspid valves involved with structural lesions.

Another helpful aid in deciding whether the two diastolic

murmurs have the same valvular cause is that the two murmurs are absolutely unlike in quality of sound.

The murmur heard over the body of the heart is a prolonged soft adventitious sound while the murmur heard above the apex is harsh and has a crescendo quality which merges with the systolic murmur that replaces the first sound at the apex of the heart.

One is justified in diagnosing, in the presence of the physical signs recited in this patient, the existence of chronic endocarditis of both the mitral and aortic valves.

We are dealing with both an obstructive and a regurgitant lesion at each valve.

A physician cannot ignore the significance of the history of the patient's father having been afflicted with the same rheumatic heart disorder.

It is becoming more and more evident to observing clinicians that "rheumatism" is, all too frequently, a "family" disease.

Before we allow the patient to dress it is well to call your attention to confirmatory evidence of the presence of an aortic regurgitation by having the blood pressure estimated.

Before we do this it is well to have one of the examiners place his finger upon the radial pulse and then raise the patient's arm above his head. By this procedure one obtains an excellent example of a pulse that has been described as a "pistol-shot" pulse, a receding pulse, the "Corrigan" pulse.

The characteristic pulse is due to the effect of the hypertrophied left ventricle's violent propulsive action in expelling its contents and the subsequent failure of the incompetent aortic valves preventing the return of the column of blood from the aorta into the left ventricle.

The blood pressure readings are 180/0.

If one listens at the elbow before the sphygmomanometer cuff is applied one will hear a loud pulse sound.

It is, therefore, impossible to estimate the diastolic blood pressure by the usual method because of its greatly decreased amount.

In patients in which there exists doubt as to the exact nature of the diastolic murmur heard over the body of the

heart it is, frequently, helpful to ascertain whether the diastolic blood pressure is normal or greatly diminished.

As is true of the majority of patients who have been unfortunate enough to contract severe and, especially, repeated attacks of rheumatism in early life this patient reveals the evidence of the presence of another very common complication of rheumatic heart affections, namely, chronic adhesive pericarditis.

The evidence of this complication is detected by inspection if one examines in a good light the posterior lateral aspects of the left chest. At each ventricular systole the marked retraction of the three lower ribs and intercostal spaces may be both seen and felt.

This physical sign, known as Broadbent's, is worthy of remembrance for if the habit is formed to seek for its presence in all rheumatic disorders of the heart it is surprising how often this characteristic systolic retraction will be found.

The visceral and parietal pericardial surfaces are adherent to each other and the parietal pericardium has grown fast to the diaphragm.

A particularly good reason for considering the presence of the systolic tugging of the left false ribs is that modern surgery, with its effective anesthetics and its delicate and efficient technic, has much to offer certain patients suffering from the effects of specific types of adherent pericardia that were not, formerly, considered amenable to surgery.

You have seen a classical example of the circulatory damage brought about by rheumatic carditis.

You will find that this disease, acute rheumatic fever, is the cause of more cases of endocarditis in patients under forty years of age than any other affection. In the northern Atlantic States this disorder is all too common and many of the worst tragedies of medical practice will be found associated with the disease, its complications and sequels.

The patient whom you have seen has been under our observation for twelve years and during that period he has remained in fair health.

On three occasions during the period named the patient had exhibited signs and symptoms of failing circulation but,

on each occasion, there has been reasonable cause for such seizures.

Each episode that the patient now describes as a "heart attack" was caused by exaggerated psychic or physical stress.

Rest in bed with the administration of opiates has been sufficient to restore the efficiency of the circulation.

Such a patient requires a sympathetic, understanding and interested physician but not necessarily a therapist.

One important psychological factor in treatment is optimism that is, all too frequently, ignored by pessimistic physicians, relatives and friends of the patient.

The attending physician must admit and face the potential dangers that such a condition of the heart causes.

What are these dangers?

They are easy to enumerate but, even under the best of economic conditions, difficult to eliminate.

The ever-present dangers are:

1. Additional attacks of rheumatism.
2. The dangers inherent in acute infections.
3. Failing compensation due to overwork as life progresses.
4. Subacute bacterial endocarditis engrafted upon the already diseased and crippled heart valves.

The physician must have these dangers ever before him, but he must not make the patient's burden of potential invalidism greater by inculcating fear that is, in many instances, a greater menace to happiness than the disease process.

To forcibly impress you with one of the ever-present dangers that such a patient encounters I have, purposely, selected the next patient.

Before having the individual brought before you I wish you to be familiar with his past medical history and to have you particularly note how similar the history is to that of the patient whom you have been studying.

Note the contrast in physical condition although the ages of the patients are, approximately, the same.

The past medical history of the 2 patients is similar to a certain point when the second patient's history becomes tragic as the result of a common complication of his cardiovascular disorder.

We are forced, as a profession, to reluctantly admit that

the sword of Damocles must hang over the health prospects of such patients but we can be happy in the knowledge that many such patients outlive two generations of physicians in spite of the ever-present hazards.

The patient whom I shall now present illustrates, all too graphically, one result of the fall of the Damoclean sword.

**Case II.**—S. J., age thirty-five, American, of Jewish parentage, has been known to our clinic physicians for many years.

At considerable inconvenience S. J. has made himself available as a "demonstration patient" before 16 successive classes of students.

There are numerous physicians established in various communities of our country who are, I am sure, much better diagnosticians than they otherwise could have been as a result of intimate observations and examinations that they were able to, repeatedly, make of the disordered cardiovascular system so cheerfully and patiently exhibited by this helpful patient.

We are indeed sorry that S. J. has, after years of practically symptomless disease, present need of our services.

If we render him as efficient help as he has given us in the past all will be well.

We have the complete medical history, previously taken, which we can read rather than fatigue an already, obviously, sick patient by requesting him to recite that which is an oft-told tale to him.

At ten years of age the man before you had an attack of rheumatic fever. This required, he states, but six weeks to "cure."

When he was twelve years old it was necessary that he spend sixteen weeks in bed with the same disorder and its complications and sequels.

When he, at long last, recovered from this seizure who can blame him for being tired of hospitals, doctors, nurses and the general atmosphere of unwelcome advice and warnings.

S. J. at thirteen years of age, without a mother to guide him, returned to an active life of strenuous athletics.

He played football, basket ball and strenuously sought to become a champion swimmer.

Who can be sure whether this inadvisable activity had

ought to do with the onset of the third attack of rheumatic fever at sixteen years of age?

Many weeks of hospitalization occurred and, shortly after his discharge from the Pennsylvania Hospital, he came under our observation.

It is well to remember that the patient's last attack of rheumatism occurred when he was sixteen years of age. He is now thirty-five years old.

We were early able to persuade him to sacrifice his badly infected tonsils upon the altar of Hygeia.

His subsequent freedom from "sore throats" and arthritic aches and pains made us and the patient feel the wisdom of prophylactic surgery.

For fifteen years the patient has considered himself in fair physical condition but, because of his strenuous work as an expressman, we were never able to, enthusiastically, share the patient's optimistic views.

The patient's wife observed in recent weeks that her husband returned from his work much more fatigued than was his custom and, contrary to his usual habit, he was willing to retire early.

The patient's body surface was hot and he had profuse perspiration during the night but he would not allow his temperature to be estimated.

At last it became evident, even to the patient, that he could not continue his work and he agreed to enter the hospital for an examination and treatment.

It was with difficulty, however, that we were able to persuade the patient to come to us in the ambulance.

We are fortunate to see this sick man on the day that he is to be admitted.

The temperature has been estimated  $101.2^{\circ}$  F., pulse 120, respirations 28.

When we glance at the eyes we see that the surrounding areas are reddened and careful inspection of the inflamed conjunctivae reveals in each small, red, painless areas, a little larger than the head of a pin.

There are painful subcutaneous spots on a finger and on one toe. These came spontaneously and without previous injury.

When we glance at the patient's neck we note the same violent throbbing of the arteries of the neck that we saw in the patient whom we have, so recently, studied.

As we expose the chest for examination those who are near can easily observe that the entire precordia is being made to forcibly pulsate, the apex beat of the heart is markedly displaced to the left and is an interspace lower than normal.

When the examiner's hand is placed over the left lower chest a marked diastolic thrill is felt and when the hand is placed over the base of the heart an even more marked systolic thrill is noted.

The pulsating carotid vessels indicate well the overacting heart action and fingers placed upon these vessels feel a marked systolic thrill.

When we auscultate the heart we find in the mitral area a to and fro murmur of marked intensity and auscultation over the base of the heart reveals an even louder double murmur.

Over the body of the heart one hears, in addition to the murmurs, a marked pericardial friction rub.

This friction rub could easily be mistaken for a double murmur but when the patient is asked to stop breathing for a few seconds one can, easily, distinguish the superficial, so-called "bread-and-butter" friction of the inflamed pericardium.

When we carefully inspect the left chest, posteriorly, we note the same tell-tale and revealing retraction of the lower interspaces that we observed in the previous patient.

The retraction is caused by a long-standing adherent pericardium firmly attached to the diaphragm.

This is a particularly interesting finding when we stop to consider that over the body of the pericardium there can, at this time, be heard evidence of a fresh pericarditis.

These findings indicate what we know to be the truth, namely, that certain areas of the pericardium may be involved in former inflammation while other areas escape.

When we expose the upper abdomen for inspection a violent pulsation of the epigastrium can be seen and we note, too, a slight bulging mass appearing below the left costal margin to the left of the midclavicular line.

This mass in the upper left abdominal quadrant descends

with respiration, is rounded and smooth and is, as you will note by the patient's expression, painful to touch.

An inspection of the right hypochondrium reveals a large and pulsating liver. This, too, is tender to the touch and its lower margin may be found at a level with the umbilicus.

The patient tells us that yesterday, while at his work as an expressman, he lifted a heavy package and felt a sudden and excruciating pain in his upper abdomen, on the left side.

He describes the sensation "as if a bullet hit me."

He was nauseated but was not able to vomit.

It was necessary for him to stop work and he returned to his home by taxicab. The pain in his upper abdomen continued, he slept little during the night and noticed in the morning that each breath exaggerated the pain in his abdomen.

On attempting to touch his abdomen he discovered the lump just beneath his left ribs. The patient states that, for some weeks, he has felt uncomfortable beneath the right costal margin but did not stop work or consult a physician. The patient informs us that, just as he was being lifted into the ambulance, he had a sudden sharp pain in the calf of his left leg.

An examination of this leg reveals no external evidence of a lesion but when one presses the calf muscle there is exaggeration and localization of the pain.

We will now allow the patient to proceed to the ward where suitable measures will be instituted to render him comfortable.

It must be evident to all of you that we have been in the presence of a brave man who has met with a medical catastrophe.

A patient whom we have observed for over fifteen years, the victim of sequels of acute rheumatic fever, practically symptomless, in spite of hard labor has developed one of the dreaded and, unfortunately, fatal complications, namely, sub-acute bacterial endocarditis.

We know that the patient has embolic phenomena in the conjunctivae, in the finger and toe, in the calf muscles and, in addition, has a large painful infarct in his spleen.

Such a combination of ills would cause the most enthusiastic therapist to pause and devoutly wish for more potent remedies.

Medical statisticians inform us that we must expect from



$\frac{1}{2}$  to 2 per cent of the patients with rheumatic endocarditis to develop subacute bacterial endocarditis.

This information illustrates well that this complication is one of the potential dangers that is inherent in the natural history of every patient we see with rheumatic endocarditis.

We must, however, hope that the first patient seen today will have better fortune than the patient we have more recently been examining.

Although this complication must be ever present in a physician's consciousness it is unfair to make the patient carry such a fear in his daily life.

The third patient that I shall bring before you illustrates another extremely common type of cardiovascular disorder.

Just as rheumatic endocarditis represents the most common type of cardiovascular disorder in patients less than forty years of age, hypertensive cardiovascular disease represents the most common variety of circulatory disease encountered in patients who have passed fifty years of age.

It should be remembered, however, that hypertensive cardiovascular disease will be encountered, all too frequently, in patients younger than forty and that rheumatic endocarditis, of long standing but unrecognized, will be, frequently, encountered in elderly patients.

**Case III.**—The patient before you is O. H., age fifty-seven, white, American.

He enters the hospital for the purpose of obtaining a "complete examination."

His chief complaints are two in number:

1. Gradually failing vision.
2. Shortness of breath on exertion.

The patient's past medical history, as given by him, is unusually uneventful. He has no recollection of previous illness and states that he has never consulted a physician.

An occasional "cold" seems the extent of his experience with illness and still it is well to be reminded that memories are not always to be trusted.

In examining this patient a few days since I noted, but did not remind the patient, the presence of two rather extensive abdominal scars.

One is in the region of the appendix and one over the site of the usual inguinal hernia.

It is a common experience to have patients entirely forget hospital experiences of long ago, even when the illness suffered was acute and painful. The taking of a good medical history is a far more difficult procedure than is the performing of a careful physical examination.

Let us see whether it is possible to add to the history as given us by this intelligent and well educated patient.

Do you have headaches?

The answer is affirmative.

When do they occur?

Chiefly when the patient is fatigued, namely, in the afternoon.

Are you dizzy at times? Yes, frequently and, at times, markedly so.

• This is, obviously, from his present statement, one of the trying symptoms that he has to endure.

How long have you noticed the dull, disagreeable sensation in the head that you hesitate to term a headache?

Between one and two years and, of late, these symptoms have been increasing.

Do you students not think that you must be able to ask intelligent questions in a way that will develop what is present but not uppermost in the patient's consciousness?

The average man dreads exaggeration of his symptoms and to avoid this, to him, great evil he is likely to understate all symptoms.

We may now list the symptoms as given:

1. Failing vision.
2. Dull, uncomfortable sensation in head in the afternoon that "some people would probably call headache."
3. Dizziness, especially when arising from the recumbent position or, even when arising from a chair.
4. Shortness of breath, duration two years, much increased of late.

What other symptoms would it be well to ask about?

Are you troubled by any urinary symptoms?

Yes. It has been necessary to rise three or four times during the night.

What of the appetite? "Nothing tastes as it once did."  
No appetite.

What of insomnia? Has slept poorly for several years. Has bad dreams. Thinks he is being smothered and wakes in a cold sweat.

This man informs us confidentially that, although he has had little personal contact with physicians he does not "like" them.

He thinks that they are not quite honest, not quite fair. It is the experience of his friends that has caused this prejudice.

Both the patient and our profession have been unfortunate in his contacts.

Before we have the patient remove his chest clothing I wish to direct your attention to easily distinguished evidences of a real need for the patient to be thoroughly examined.

What does the student associate feel about the appearance of the temporal vessels?

The patient states that his father had similar prominent temporal vessels. His father died of "a stroke" at sixty-one years of age "while in perfect health." Apoplexy "runs in the family."

When we bare the arms it is obvious that the brachial vessels and their branches are both more superficial and more strikingly evident to the eye. When we feel the brachials there is evidence of more thickening and more resistance to pressure than is usual.

The student seated opposite this well built but emaciated man will give us his impression of the size of the heart.

The apex is in the fifth interspace but it is displaced to the left a distance of at least 2 inches from the normal site.

How does the cardiac area feel when the hand is placed over it?

There is a decided increase in the heart impulse and at the apex there seems to be "an impulse so strong as to give the sensation of a systolic thrill."

At the base of the heart is a marked diastolic shock. To determine this one needs only to place a finger on the apex beat or upon the carotid vessel and note that the shock is

not synchronous with the ventricular contraction but occurs immediately after.

This shock is due to the violent closure of the aortic valves when the column of blood in the aorta finds a lack of elasticity in the artery and attempts to return into the ventricle through the competent aortic valves.

When one listens to the mitral area one hears a loud systolic murmur. This murmur is, I feel sure, not due to an endocarditis because there is no history of the etiologic disorder, but is due to the stretching of the mitral valve orifice by the hypertrophy and dilatation of the left ventricle.

Over the aortic area one hears a slight systolic murmur but in diastole there is a sharp, loud and almost metallic snapping sound.

The pressure within the brachial vessels is greatly increased, 280/160.

When we have the patient recumbent I wish you would, particularly, note the violent pulsations of the femoral vessels.

When these vessels are palpated we find them in the same tense condition that is shown by the vessels in the upper extremities. It is entirely unnecessary to cause the patient the expense of visualizing the sclerosis of the arteries by roentgen ray examination.

We should, by constant practice, educate our fingers to the varying feel of normal and abnormal blood vessels.

The patient whom we have examined will come to no harm by admitting him to the medical ward for a bed rest and during his stay he can be thoroughly studied.

The eyegrounds will be, particularly, examined as to the state of the vessels.

Physiotherapeutic measures with restful and relaxing massage will prove, in my judgment, of greater value than drug therapy.

Can we be sure that had we studied this patient fifteen years ago and had he been willing to adopt all of our well meant suggestions for the prophylaxis of vascular pathology that the result would have been so different from what we find today?

There is a well-founded tradition in this man's family that the males die before sixty of vascular accident.

Heredity is, as far as we at present know the most im-

portant single etiologic agency in the disorder known as hypertensive cardiovascular disease.

We know far too little of direct causes, other than lead and other chemical poisons, but it is believed that constitutional deficiencies and the wear and tear of life, especially the emotional stress, have both direct and indirect bearing upon the development and continuance of the extremely common disorder. What are the greatest potential dangers to the patient we have dismissed? Cerebral accidents, hemorrhage or thrombosis, on the one hand and gradually developing failing compensation of the cardiovascular apparatus on the other.

In an age in which man's existence is prolonged to a greater length than at any time in history the medical profession must be prepared for the perfect understanding of the symptoms and signs of an ever-increasing number of chronic degenerative cardiovascular disorders.

Medical students, graduate or undergraduate, cannot be reminded too forcibly that to be of real help to elderly patients one must understand the psychology of oncoming age as well as to be entirely familiar with the physical evidences of senescence.

An intimate familiarity with the mode of thought of aging persons in good health will clarify the problem of the care of the aged sick.

The next and last patient to be shown in today's clinic illustrates another common cardiovascular disorder.

**Case IV.**—J. McN., age forty-seven, white, American of Irish descent.

His chief complaint is that, recently, he has periods, especially at night, when he is unable to "get a good breath."

One glance at the man and you can see that, in his younger years, this man was an athlete.

He has all the appearance and posture of a man who was sure of his body strength.

What has happened to cast doubt in his mind regarding his present state of health?

The history as recited in the dispensary is, to a great extent, negative as far as physical illnesses is concerned.

When he arrived in this country from Ireland he was em-

ployed as a coachman, later as a chauffeur and, more recently, he has been employed as a doorman at one of the fashionable apartment houses of our city.

With premeditation I have accepted the history as given in the dispensary as approximately correct and have asked the patient to appear before you to illustrate a very commonly misinterpreted clinical entity.

The patient's story is suggestive. He was "absolutely well," to use his own expression, until six weeks ago.

At the apartment house where he is employed disturbances are rare but on the night that he developed symptoms of his present malady it was necessary for him to use all his physical strength, plus his reserve energy, to quell a maniacal alcoholic.

This patient succeeded in a difficult and, let us remember, thankless task where a number of men, in cooperation, had failed but during the strenuous struggle with his opponent he felt, as he terms it, "something give way in my chest."

He was weak, nauseated and states that "everything became dark before my eyes."

The patient continued at his work which consisted in opening auto doors and, frequently, using his strength in opening the heavy door of the apartment house.

He had a dull pain over his upper sternum that was relieved in part when he went to bed.

He returned to his work the morning after the episode of physical struggle but since that time has not been in his usual health and good humor. He has consulted several physicians regarding the troublesome pain in his chest who assure him that he has "strained his heart" and that, if he will go slow, all will return to normal.

Three days ago this patient appeared at the dispensary and we were fortunate enough to have him appear before a small section of the class.

There now appears an opportunity to reveal to the larger group the physical signs, emphasize the history, and call attention to the need of imagination in medicine.

Before we delve into the past medical history let us, together, study the physical signs that are so revealing.

The first student calls attention to the fact that there is an

obvious, abnormal pulsation in the neck superior to the junction of the clavicles.

This pulsation of the innominate artery attracts more attention than does the less obvious but distinctly abnormal pulsation of the carotids.

The second student finds that, in spite of the well-muscled and overplump chest of the patient, he can, without difficulty, both see and feel that the apex beat of the heart is displaced far to the left of the normal position and the left border can be easily palpated.

There are no thrills to be palpated but one notices that the patient winces with discomfort if too heavy a hand is used in examining the precordia. Auscultation reveals a systolic murmur at the cardiac apex and another and louder systolic murmur at the aortic cartilage and transmitted into the vessels of the neck.

In this particular patient it is well to point out that no examination of the cardiovascular apparatus can be considered complete unless one has examined the subject in the sitting, recumbent and in the standing, sitting or recumbent position after exercise.

We will ask another student to first confirm the position of the heart before he listens to its sounds and to exclude the possibility of its abnormal position being due to displacement due to pressure from the right pleural cavity.

The student is satisfied that the heart is hypertrophied and suggests that it is also dilated.

The obvious fact that the lips are distinctly cyanosed bears out the latter impression.

The student states that he hears the systolic murmur at the apex and base without difficulty when the patient is in the recumbent position but I notice that he has only auscultated the localized valve areas over the body of the heart and has not, particularly, auscultated over the remaining body of the heart.

When he listens over the left side of the sternum at the fourth costal cartilage he hears a soft murmur which he believes is not synchronous with ventricular systole as ascertained with his finger on the innominate pulsation.

We will ask the next student to confirm the accuracy of

the timing of the murmur. He is agreed that we have the presence of a diastolic murmur over the body of the heart.

You will note that, despite the fact that the patient had two pillows to lie upon, he is relieved to be allowed to sit upright.

To spare the time of the assembled group I ascertained with certainty that the patient's history is free from the usual causes (namely, rheumatism) of valvular endocarditis.

We will have the blood pressure estimated and the student assures me that although the systolic blood pressure varies more than he thinks it should from moment to moment that it approximates 160.

When he attempts to take the diastolic pressure he is disturbed to find that this is even more difficult to be sure of but that the vascular sound in diastole disappears at, approximately, 40 mm. and that, occasionally one can hear the sound as low as 10.

We then have a patient before us that exhibits the classical physical signs of aortitis with aortic regurgitation and resulting hypertrophy and dilatation of the heart.

A frank talk with the patient regarding the possibility of a venereal disease in his younger years is productive of equally frank statements on his part. When he was twenty-two years of age, and while under the influence of alcohol, he exposed himself for the first and only time in his existence to the possibility of venereal disease.

Some four weeks following exposure the patient developed a small, hard sore on his penis that persisted until "a druggist" gave him an ointment to use and, from that time, twenty-five years ago, he has never had a symptom of disease nor, as far as he is aware, has his general strength failed.

We have, gratefully, called upon the laboratory for help and they return word that both the Wassermann and Kahn reactions of the blood are strongly positive.

We are dealing with a luetic aortitis with resulting incompetence of the aortic valve and the history strongly suggests that physical strain brought about the incompetence of the valves that, under ordinary circumstances, might never have appeared.

Luetic cardiovascular diseases exist in every community and the recognition of them depends upon a physician possess-



ing "a high index of suspicion" as to the nature of obscure and unusual cardiovascular manifestations.

No one, other than the physician, has the right to invade the privacy of a patient's ancient and well hidden memories and no one, better than can the doctor, advise against irregular sexual contacts.

The proper understanding and the efficient treatment of this condition must depend upon correct etiologic diagnosis.

Does our duty as physicians stop here? Through the family physician we can, perhaps, aid in throwing light upon a chronic state of invalidism in the patient's wife. There are, perhaps fortunately, no children in this man's home.

His wife, the patient assures me, was the picture of health when she was married but, following several miscarriages, she has, according to the husband's statement, "entered a decline" and is far from well.

**Summary.**—We have studied 4 patients together by the classical method of careful history taking, painstaking physical examination and the laboratory help that one finds available in one's office, namely, blood pressure estimations and urine examinations.

We believe that any well-trained physician who will take the time and devote the thought necessary to make such a systematic survey of his own patients is, in the majority of instances, the safest and best guide for the average patient.

Postgraduate work can be carried out in one's own office and with one's own patients as study material with lasting benefit to both patient and physician.

Each physician has the opportunity for being a more vital influence upon the lives of his patients than any individual with whom they come in contact.

Our opportunities are unexcelled and our responsibilities are, equally, great.

It is helpful to bear in mind that the patient is far more important to understand than is the disease process that affects him or her.

Thorough examinations, carefully kept notes of observations and findings and continued interest in all unexplained symptoms make us worthy of our professional heritage.

May each of us do the day's work as well as we know how. May each keep ever before us the desire to do tomorrow's work more efficiently than today's.

If every physician practiced his art with the thought of the Golden Rule in mind there would be fewer insoluble professional problems.

## CLINIC OF DR. CHARLES C. WOLFERTH

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### THE DIAGNOSIS AND TREATMENT OF ACUTE CORONARY OCCLUSION

**Diagnosis.**—Coronary occlusion is sometimes discussed as though it were an independent disease entity. It is really a by-product of some pathologic process involving a coronary artery. Excluding the rare occurrence of embolism, this objectionable by-product results from disease of the artery itself. Various types of arteritis, of which the most important is syphilis, account for a small minority of cases; the vast majority are incident to coronary arteriosclerosis.

There are two major clinical patterns, one corresponding to an acute and the other to a chronic condition. Each pattern is subject to such variation that its recognition is often difficult. Moreover, combinations of the two are constantly encountered. There is one symptom inseparable from both—impairment of cardiac function—which may be so severe as to cause death, or so slight as to go unnoticed by the patient. The acute process is exemplified by the patient who is seized after little or no warning with intolerable constricting substernal pain, requiring large doses of morphine, for relief. He may die suddenly at any moment. If he survives, he is apt to develop, in the course of a day or two, severe heart failure with small, feeble pulse and pulmonary congestion, fever and leukocytosis. In the typical chronic process, heart failure comes on gradually, sometimes over the course of many years. Such phenomena as angina pectoris, paroxysmal nocturnal dyspnea or disturbances in cardiac rhythm may occur. At necropsy both these clinical types may be found to have coronary occlusion in similar locations. If we ask ourselves the reason for the remarkable difference in the behavior, the

only explanation available is that it depends on the rapidity of development of the occluding process and the efficiency of collateral circulation. Most, but not all, of the patients who suffer from an acute stormy attack are found to have had acute thrombosis superimposed on a gradually developing occlusion resulting from arteriosclerosis. This has led to the use of the term "coronary thrombosis" in connection with these attacks. The term is not entirely satisfactory for two reasons: (1) thrombosis, although it may precipitate the acute attack, is but the capstone in the process of occlusion, and (2) thrombosis cannot be found, and presumably has not occurred, in some of the patients who have suffered acute attacks. In the patient with no acute painful attacks except paroxysms of angina pectoris and in whom death results from gradual heart failure, coronary artery thrombosis is not often found at necropsy. Moreover, such a heart rarely shows massive infarction but there is apt to be a mixture of scar and muscle tissue. These differences are foreshadowed by differences in the electrocardiograms in the two types of cases. Although all coronary arteriosclerosis marches relentlessly toward cardiac failure, the cases in which acute episodes are superimposed on the slowly developing arterial process are apt to have a more disastrous course. This is because of the greater damage to heart muscle and the fact that this type of acute damage frequently leads to sudden death (ventricular fibrillation, cardiac rupture or embolism).

A factor that doubtless influences the course of events after coronary occlusion is the condition of neighboring vessels. There is some evidence to indicate that when infarction develops it may depend not only on the size of the artery occluded and the rapidity of occlusion, but also on the patency of the vessels supplying the surrounding area.

One question of considerable interest is the relationship of size of vessel occluded to the production of symptoms. A few years ago, Dr. F. C. Wood and I noted in animal experiments, which included clamping of coronary arteries, that the occlusion of small branches caused injury currents great enough to manifest themselves in the electrocardiograms. It is well known that occlusion of very small vessels without clinical heart disease is common after middle life. The thought has

often been expressed that some minor attacks now labeled angina pectoris, although usually lasting longer than angina and not precipitated by exertion, are really due to occlusion of small arteries. Some of the minor seizures of pain prior to a major attack of coronary occlusion may be of this nature. Sometimes minor and relatively transient electrocardiographic changes are observed in association with such attacks suggesting at least slight acute muscle damage.

The most prominent symptom of acute coronary occlusion is pain. It occurs in nearly every case in which infarction, sufficiently large to be demonstrated by electrocardiogram, is present. Its characteristics have been described so often that it seems unnecessary to repeat them here. A few comments, however, may not be amiss. (1) The pain is not always agonizing or intolerable. The patient may continue at his work thinking he has indigestion or some sort of congestion in his chest. Centering of the pain in the lower substernal or epigastric region, especially when temporary relief is produced by eructation of gas, strengthens his belief that he has indigestion. (2) If a patient subject to attacks of angina pectoris develops a pain of the usual type, which, instead of subsiding promptly, lasts an hour or more, the possibility of coronary occlusion should be considered. Sometimes, however, patients subject to angina pectoris describe the pain during an attack of coronary occlusion as somewhat different in location and quality, as well as intensity and duration. (3) Although the pain is usually centered in the substernal region, with or without radiation, it may be greatest in the precordial region, the upper left breast, shoulders or arms (usually the left but occasionally the right or both), the neck or under the left scapula. There may be a complaint of mid or lower abdominal pain, but if maximum intensity of pain is in these areas, it is due to something other than coronary occlusion. Severe upper right quadrant pain is rarely if ever due to coronary occlusion, although some tenderness and pain may develop in this region following an attack, due to congestion of the liver. (4) Studies made with Dr. F. C. Wood in the attempt to correlate location of pain with site of infarct have yielded negative results. (5) The location of pain apparently has some bearing on its quality. The usual terms used in describing the

pain are that it is "constricting" or "viselike," "burning" or "boring." Upper substernal pain is often described as choking rather than constricting. Pain in the upper left chest or back is apt to be burning or boring. Pain in the shoulder, arm or jaw is often described as an intolerable ache. Pain in the precordial region may give a sensation of fulness—as though something had become too large.

One of the differences between angina pectoris and coronary occlusion is that after an attack of angina, the patient is apt to feel very much as he did before except that nervous individuals often suffer from exhaustion as they do following various sorts of experiences; usually, however, during the days following coronary occlusion with myocardial infarction, the patient looks sick, even though his attack of pain had been mild and he has continued working or at least has remained ambulatory.

Fall in blood pressure may be quite prompt or it may be delayed twenty-four or forty-eight hours. The other well-known evidences of infarction such as friction rub, pulmonary congestion, fever, leukocytosis and acceleration of sedimentation rate tend to make their appearance within the first three days.

The diagnosis can be made clinically with a high degree of accuracy in typical cases of acute coronary occlusion with myocardial infarction, particularly after a few days' observation. Many cases, however, are atypical; furthermore, the need for prompt differential diagnosis may be urgent. Under these circumstances, additional evidence is required, and this is furnished by electrocardiography. It is necessary to bear in mind, however, that the diagnosis of coronary occlusion, *per se*, cannot be made from the electrocardiogram. All the tracing can be expected to do is to reflect, more or less imperfectly, the electrical activity incident to the heart beat. Coronary arteries obviously take no direct part in the heart beat, although they supply the blood which makes it possible. Acute disturbances in this blood supply are apt to cause changes in the action currents of the myocardium which are revealed by changes in the electrocardiogram. Thus, the electrocardiogram yields only indirect evidence of coronary occlusion. However, it has been learned that acute myocardial infarction

tends to cause characteristic electrocardiographic patterns which, considered in connection with clinical findings, make the diagnosis of coronary occlusion practically certain. In some cases, however, the findings on the first electrocardiographic examination are inconclusive; under these circumstances, tracings must be repeated. Rapidly changing electrocardiographic patterns, provided extrinsic causes such as drug effects are excluded, reflect rapid changes in the myocardium and may therefore furnish evidence of coronary occlusion even though the complete pattern of infarction does not occur.

During the past five years since we have used chest leads to supplement limb leads in electrocardiography, it has been found that if the clinical picture suggests coronary occlusion with myocardial infarction, and the electrocardiogram fails to confirm the diagnosis either by showing one of the typical patterns or by rapid changes, the clinical diagnosis of infarction is almost certainly incorrect.

Electrocardiography also has considerable value in the diagnosis of the chronic or healed stage of myocardial infarction. This is particularly true of infarction involving the anterior wall of the left ventricle. A pathognomonic electrocardiographic pattern may persist for many years, although it often tends to fade out in time. The chest leads furnish an essential part of this pattern. When infarction occurs in other locations, the electrocardiographic pattern cannot be regarded as pathognomonic, although when considered in relation to the clinical history, it may be helpful in the diagnosis of old infarction.

A problem the practitioner has to face when dealing with a patient in whom he suspects the presence of coronary occlusion, is whether or not to have an electrocardiogram made. There are two reasons to make him hesitate: (1) the expense to the patient, and (2) the possibility that an electrocardiogram may not help in the diagnosis but may actually lead to an incorrect diagnosis.

So far as the expense is concerned, it should cost no more to have an electrocardiogram made than a roentgen ray examination for suspected fracture, and even less if the examination is made at the patient's home. The importance of determining the presence or absence of coronary occlusion is

at least as important as recognizing fracture. Regarding the possibility that an electrocardiogram might actually lead to an incorrect diagnosis, some of the previous discussion is pertinent. There is no valid reason why an electrocardiogram, properly made and interpreted, should obscure the issue. Nevertheless, experienced workers in the field of heart disease not infrequently see cases in which electrocardiography has been responsible for a wrong diagnosis. Such errors are liable to be disastrous.

There are various reasons for incorrect interpretation of electrocardiograms: (1) the technic of taking the tracing may be incorrect. This has been discussed so often that it should not be necessary to repeat it here. It may be pointed out, however, that in taking chest leads, the relative positions of a precordial electrode and the heart itself are important. Most of the work on standardization of tracings has been done with the electrode applied as nearly as possible to the apex. (2) The person interpreting the tracing may not be competent to interpret electrocardiograms. The remedy for this is obvious. (3) There may be failure to take into account all the factors necessary for electrocardiographic diagnosis. This is a far more common source of error than faulty technic or actual incompetence in interpretation. On logical grounds one might contend that electrocardiographic and clinical diagnosis should be completely divorced. There is no reason why the electrocardiographer may not attempt an independent diagnosis as a preliminary procedure, if he so desires. He is on safe ground so far as the recognition of cardiac arrhythmias is concerned and also in cases showing the typical complete pattern of myocardial infarction. However, for adequate interpretation, consideration of all relevant data is essential. It is important to know whether the patient has taken digitalis, and, if so, the details of dosage. Such diverse factors as position of the heart, disturbances of thyroid function, the blood pressure, recent or active infection or debilitating disease or even certain nervous states may be cited as examples of conditions that need to be taken into account. In cases suspected of coronary occlusion, it is particularly important that the entire clinical history should be reviewed so that all possible sources of error of interpretation receive consideration. Furthermore, if the



electrocardiogram does not support a clinical diagnosis of acute coronary occlusion, tracings should be made with an electrode on various parts of the precordium in an effort to detect injury currents. Two or three electrocardiograms a few days apart may be required.

In summary it may be said that the diagnosis of acute coronary occlusion depends first of all on careful history, examination and sometimes repeated observations. Electrocardiograms, including chest leads, should be made in all cases in which the diagnosis cannot be excluded by clinical study. In some cases serial electrocardiograms are required. The interpretation of electrocardiograms should not be relegated to a technician, whether or not he has a medical degree. The tracing should be interpreted with full knowledge of all relevant clinical data available. If these conditions are met, a physician familiar with the manifestations of acute coronary occlusion and conditions which may simulate it should make few mistakes in diagnosis.

**Treatment.**—The first thing to do in an acute attack is to relieve pain if it is severe. Morphine is probably the most effective agent for this purpose, although pantopon or dilaudid may be used. The physician must depend on his judgment as to how much morphine is required. In some cases a single hypodermic injection of  $\frac{1}{6}$  to  $\frac{1}{4}$  grain is adequate. In others, several injections may be required. The use of morphine is sometimes overdone; I have often suspected that the last unnecessary dose precipitated a fatal outcome. One does not need to give enough of the drug to abolish pain completely, although it should be made bearable. Some patients continue to complain but if let alone will promptly drop off to sleep. The application of heat all over the front of the chest is often helpful and may lessen the amount of morphine required.

The patient should be moved as little as necessary during an acute attack. If at home he should stay there unless it is impossible to care for him. He should be placed in bed immediately and, in addition to the use of measures for the relief of pain, he should be kept warm. He should not be annoyed by too many attentions. The illness should not be regarded as a social event calling for the presence of a large gathering of relatives and friends. Nevertheless he should be watched

every moment by a responsible person. Frequent hypodermic injections of supposed cardiac stimulants are very comforting to the family and give them a feeling that something is being done. It would be better for the patient, however, if most of these treatments were distributed among the members of the family who want action. Concentrated glucose solutions by the intravenous route may have some value in relieving pain and helping to support the circulation. It is desirable that further critical study be made of this procedure. Intravenous injections of aminophyllin are recommended by some writers although its value is not yet established. It is said to have been highly effective in relieving pain in certain cases.

The oxygen tent is being used more and more in the treatment of acute coronary occlusion. Oxygen seems to have some value in relieving pain although the results are not spectacular. It is also useful if there is shortness of breath or cyanosis.

Treatment must be individualized not only during the initial stages but thereafter as well. All patients should be kept in bed, but concessions must occasionally be made to those unable to use a bed pan successfully. These patients may be permitted to use a commode by the side of the bed. How long patients should be kept in bed is largely guesswork. Probably those without definite evidence of infarction, or only slight evidence of infarction and favorable clinical course, may be permitted to begin sitting out of bed in four weeks. Some patients must be kept in bed for much longer periods. In such cases the course of the erythrocyte sedimentation rate may be helpful. A return to normal rate may be interpreted as a favorable finding.

The care of the gastro-intestinal tract is important. During the time the patients feel ill, there is usually little disposition to eat heartily. In any event, however, it is well to keep the diet low in bulk and caloric value. Frequent small feedings, 4 to 6 daily, are preferable to normal-sized meals. Distention is often a troublesome feature. It may be treated by the application of heat or turpentine stupes, rectal tube, daily enema, or small doses of salines or castor oil. Drastic purgation or pituitary extracts would better be avoided.

Sleeplessness is often a problem. If it is due to cough, shortness of breath or discomfort in the chest, codeine or a

small dose of morphine is apt to be effective. Otherwise bromides or small doses of barbiturates may be tried.

The question always arises as to whether aminophyllin should be used. Animal experimentation appears to show that it is an effective coronary vasodilator. Furthermore, it has been maintained that myocardial infarction produced in animals by ligating coronary vessels is apt to be less extensive if aminophyllin is given throughout the period of the experiment. These facts afford a logical basis for its use. Nevertheless, considerable experience in giving the drug has thus far failed to convince me that it has much value in the treatment of acute coronary occlusion. Furthermore, some patients do not tolerate it well. The gastric symptoms are well known. It may also cause bladder irritability, restlessness and cardiac palpitation.

Physicians often ask what they should do in the event of sudden collapse of a patient who has suffered coronary occlusion. Sudden collapse may be due to one of a variety of mechanisms. In dogs, sudden death, following ligation of a coronary vessel, is practically always due to ventricular fibrillation; there is reason to believe that this is the most frequent cause of sudden death in patients who have suffered acute coronary occlusion. When ventricular fibrillation occurs, it is probable that events move too quickly for therapeutic action even though any could be effective. Embolism from an intraventricular thrombus or rupture of the infarct may also cause sudden death. However, as is well known, the patient may survive embolism unless it deprives a vital structure of its blood supply. Furthermore, if an infarct ruptures through the intraventricular septum, the patient may survive. These two conditions may, but do not always, cause sudden collapse. The onset of paroxysmal tachycardia, of which the most common is paroxysmal auricular fibrillation, may also cause collapse, particularly in seriously ill patients. However, many patients suffer collapse without any obvious cause except circulatory failure. The value of various restorative procedures in the treatment of sudden circulatory failure is not clearly established. Intramuscular injection of caffeine sodium benzoate and intravenous injections of concentrated glucose solutions at times appear to have some value.

The question of digitalis therapy in the treatment of acute coronary occlusion is frequently raised. There are at least two indications for its use: (1) prolonged paroxysms of auricular fibrillation, and (2) severe heart failure threatening the patient's life. It must be given cautiously since there is reason to believe that full dosage of digitalis is apt to be dangerous. On the other hand, the effect must be prompt if it is to do any good at all. A modification of the Eggleston method, administering half the recommended dosage during the first twenty-four-hour period, may be used. Fortunately, only a small minority of cases require digitalis.

Some observers favor the use of small doses of quinidine two or three times a day in the hope that it will prevent ventricular fibrillation. Its use at the present time is empirical. We do not know with any certainty, whether quinidine will prevent ventricular fibrillation in patients with coronary occlusion, nor if it does, what dosage is necessary or what other undesirable effects it might produce in these very ill patients.

One of the most important duties of the physician is guidance of the patient after allowing him out of bed. The objectives at this time are to do everything possible to help him to recover his strength and to prevent recurrent attacks. The procedures are empirical. It seems sensible to increase activities slowly and well within the limits of the individual's tolerance. He should accept restrictions in his regimen. If he complains about this, one may reply that his former way of living led him into trouble; that if he wants to cooperate in the attempt to avoid further trouble of the same nature, he must live differently. This includes abstemious habits of eating, care of the gastro-intestinal tract, abundant rest and relaxation, and cutting down on work to the point where hurry and the tension that goes with it, are eliminated. There is little knowledge but much difference of opinion regarding the effects of tobacco and alcohol. Under these circumstances, it seems prudent to adopt an attitude of caution. After all, one cannot go far wrong in counseling good habits.

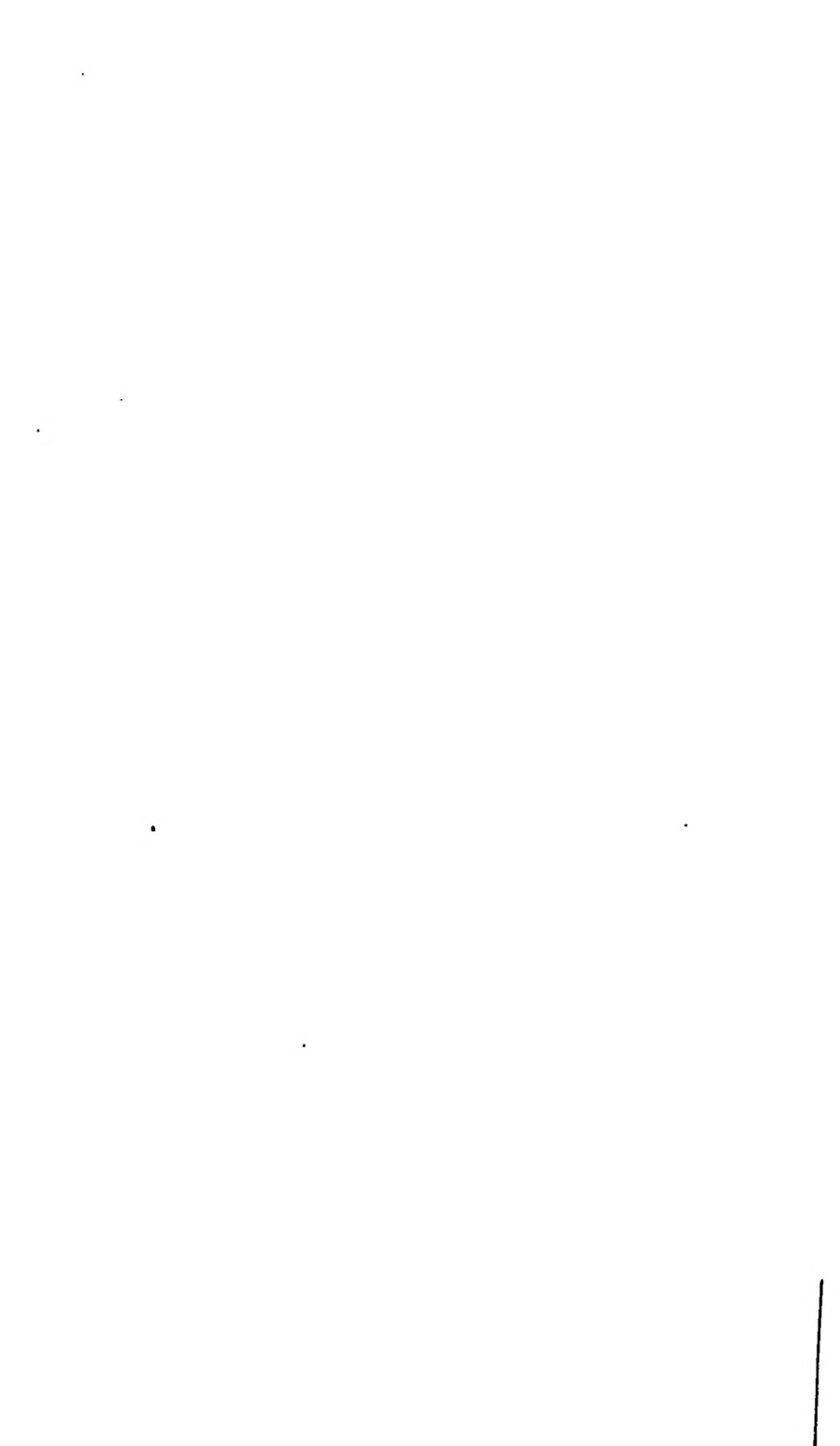
The following points may be made regarding alcohol: while small amounts of alcohol late in the afternoon or before dinner may be useful in certain individuals, it should not be taken before meals by those who have difficulty in curbing

their appetite for food, nor by those in whom it has a tendency to disturb the gastro-intestinal tract. Liberal consumption of alcohol is unwise, if for no other reason than its tendency to make the user relax his regimen in other directions.

There are some statistical data which appear to show that tobacco is of little or no importance as a cause of coronary occlusion. There is no doubt that coronary occlusion may occur in individuals who have used only small amounts of tobacco or none at all. On the other hand, it seems to occur often in those who have been persistently heavy smokers over long periods of time. However, even if a statistically significant relationship could be established, it would not necessarily prove that tobacco had caused the coronary disease or accident. It might be that some underlying nervous or metabolic tendency had been responsible both for the heavy smoking and the arterial disease. However, excessive use of tobacco does cause a tendency to fatigability, increased pulse rate and irritation of respiratory mucous membranes and in some individuals increased nervous tension, disturbance of gastro-intestinal functions and increased consciousness of heart action. Certain patients state that their tendency to attacks of angina pectoris is distinctly less when they do not smoke, although many note no difference whatever. In view of these facts, I think that an attempt should be made to have patients avoid tobacco after an attack of coronary occlusion or at least use it sparingly.

It has seemed to me that in general those patients do best who accept their handicaps philosophically and at the same time lead a careful life, avoiding bad habits and excessive nervous or physical strain. Those who are able to retire from active life and are content to do so, should be encouraged in this course. Those who are unable or unwilling to retire, should review their activities carefully and prune out the non-essentials.

Follow-up studies in patients who have suffered from coronary occlusion show that the liability to recurrent attacks is great and that the expectation of life is far from good. Nevertheless, some individuals do well and are able to carry on for a number of years. It is often helpful to recount instances of such favorable cases to despondent or apprehensive patients and try to encourage them to a more hopeful frame of mind.



## CLINIC OF DR. HENRY K. MOHLER

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#### MISSED CARDIAC DIAGNOSIS

CARDIAC disease is difficult to diagnose at times because it has symptoms which are common to many other functional and organic disturbances of the body. Among the disorders resembling heart affections are those arising in the pulmonary, renal, and vascular systems and in the gastro-intestinal and biliary tracts. Dysfunction of the thyroid gland frequently is reflected in disorders of the heart. The increasing morbidity and mortality as a result of cardiac disease constantly are challenges to the medical profession to bear in mind the need for differentiating diseases of the heart from conditions resembling them. Functional diseases of the heart must be separated from organic disease to prevent unnecessarily restricting physical activity where not warranted.

The failure to obtain a detailed history and not infrequently the lack of a complete study of the patient can be responsible for missed diagnoses. Inadequate facilities may account for failure to recognize cardiac disease. A typical history, symptoms, physical findings and an electrocardiogram readily make possible a correct diagnosis of an acute coronary occlusion. The atypical case is one in which a correct diagnosis may be missed.

Signs and symptoms of importance may be transient and often absent at the time of examination. The physician, therefore, lacks possession of sufficient evidence to make a correct diagnosis. Pain in the chest may be incorrectly interpreted as being due to some disease other than of the heart.

Failure to diagnose conditions subsequently proved to be cardiac in origin may prove very disastrous. An attack of acute coronary occlusion allowed to become ambulatory after

the gastro-intestinal features subside may result fatally, because the condition was diagnosed as acute indigestion. In other instances the functional disturbances in the mechanism of the heart may be considered as serious. Numerous restrictions unnecessarily imposed upon the patient, especially as to physical activities, may continue a cardiac neurosis.

It is extremely difficult at times to obtain an accurate description of the character of the pain or abnormal sensations complained of by the patient. Thus is emphasized the importance of continuing at length the discussion of the symptoms as to their character, location, duration and factors bringing on the distress or pain, its relation to effort and rest and whether it comes on during sleep. Pain or discomfort of a serious nature is usually substernal in location and accompanied by dyspnea if it is cardiac in origin.

If this substernal pain is precipitated by effort and is of short duration and is relieved by rest or by the taking of nitrites, the diagnosis of angina pectoris can be made without much doubt and a cardiac diagnosis not missed.

Pain or distress of a similar nature not brought on necessarily by effort, continuous, not relieved promptly by rest, or by the use of nitrites, and associated with shock and dyspnea, must be regarded as probably due to acute occlusion of the coronary artery. Within twenty-four hours this patient will have developed a systemic reaction to the interference with the coronary circulation manifest by an ashen gray color of the skin, the presence of fever, a leukocytosis, a variation in the pulse rate, usually increased (occasionally slow due to an accompanying heart block) with or without an arrhythmia. The systolic blood pressure gradually becomes lower. The presence of these symptoms and signs with a full knowledge of the nature of its onset with the presence of serial electrocardiographic changes in the RST complexes and T and Q waves warrants a definite diagnosis of acute coronary occlusion. The diagnosis may be missed if the patient comes under a physician's care without being given a clear history of what transpired previously—as an example:

M. A., age fifty-four years, longshoreman, brought to the receiving ward of the hospital, giving a rather incoherent his-



tory of having had an attack of grip during the previous week and of being given whisky and quinine to relieve his symptoms, which were cough and general chest pains. The physical examination revealed nothing but the presence of numerous small râles throughout both lungs, but no definite area of consolidation. His temperature was  $101.4^{\circ}$  F., the pulse rate was regular and 100 per minute and the blood pressure 140/100. Albumin and granular casts were present in the urine. The leukocyte count was 11,000. The patient seemed to improve clinically but the fever and the cough continued and two days after admission he died suddenly. Autopsy showed a ruptured heart through an area of infarction of the anterior wall of the heart. The patient was too ill to give a clear history of the onset or attached little importance to the substernal distress, if present at the onset of his illness. The heart during life appeared normal on physical examination.

**Dyspnea**, sudden in onset and gradually improving with rest in bed, may be the only initial important symptom and so overshadow the substernal pain (which if present), was not severe enough to be recognized by the patient. A leukocytosis, an increased pulse rate and a declining previously known high systolic blood pressure may be evidence of an acute coronary artery occlusion.

Nocturnal dyspnea severe enough to cause a patient to sit up in bed to secure relief, accompanied by wheezing sounds in the chest may, unless promptly reported to a physician, be diagnosed bronchial asthma. The symptom-complex of fever, leukocytosis, shock, prostration and ashen gray color of the skin following this nocturnal attack of dyspnea should make one suspicious of the presence of coronary artery occlusion. Dyspnea occurring during the night with hypertension, unless thought of and measures taken to restrict physical and mental activity may be a forerunner of acute coronary occlusion.

**Tachycardia with or without the Presence of Arrhythmia.**—A young adult complaining of tachycardia, with or without evident enlargement of the thyroid gland may be incorrectly diagnosed hyperthyroidism. Two or three basal metabolism tests usually are helpful in determining if the thyroid gland is overactive and hence responsible for the tachycardia. In a number of cardiac patients auricular fibril-

lation may be present, with or without symptoms and signs of congestive heart failure. The increased heart rate as a result of hyperthyroidism often is responsible for the onset of auricular fibrillation. The effective treatment of hyperthyroidism results in slowing of the heart rate and usually normal sinus rhythm returns. The administration of quinidine sulfate is often helpful in restoring a regular rhythm. Should the classical treatment usually effective for the hyperthyroidism fail, one can usually be certain the tachycardia is due to myocardial weakness rather than to an overactive thyroid gland, even though a goiter be present with only a slightly elevated basal metabolic rate.

Tachycardia occurring in paroxysms, sudden in onset, not influenced by posture and sudden in cessation is correctly recognized as simple paroxysmal tachycardia usually not associated with organic heart disease, but may accompany acute coronary occlusion.

The heart rate which is irregular in force, rate and rhythm, becoming increasingly so by effort after showing a pulse deficit in the untreated patient is due to auricular fibrillation.

Premature contractions are responsible for an irregular rate depending on the frequency of their occurrence. They may be recognized at times by their disappearance with exercise and reappearance when heart rate becomes slower. This is not uniformly so, especially if they are associated with organic disease of the heart and hypertension.

A less common occurring tachycardia is sudden in onset, usually associated with marked coronary sclerosis or with acute coronary artery occlusion. This form of rapid heart rate is known as paroxysmal ventricular tachycardia and is recognized by the occasional interruption of the tachycardia by missed beats or a weakness of the heart sounds noticed only by auscultation. The recognition of this arrhythmia is important because the use of quinidine is often effective in causing the condition to disappear.

**Pulmonary Edema.**—Patients may become dyspneic with subsequent cough which quickly becomes productive, frothy and blood-stained and is accompanied by other alarming symptoms. Signs of acute myocardial failure result fatally in a brief space of time from acute pulmonary edema.

These patients on previous occasions may have suffered mild attacks of cough, dyspnea and wheeze to which they paid little attention, believing it to be asthma, but which eventually proved that the left heart failed with an accumulation of edematous fluid in the lungs. Recognition of this possibility will avoid missing cardiac diagnosis.

**Psychoses.**—An active middle-aged patient, without a definite history of substernal distress or pain, presenting a psychosis, sudden in onset, especially if accompanied by symptoms of shock and an ashen gray color of the skin may be the result of a disturbance of the circulation of the blood due to an attack of acute coronary artery occlusion.

The history of previous attacks of substernal pain probably anginal in nature followed by the clinical picture of a psychosis may be shown by electrocardiographic examination to be due to the presence of an acute coronary infarction.

Many of the psychoses give a history of recently having passed through a period of mental shock and strain. Such etiology can be responsible for both conditions and one can readily fail to recognize an attack of coronary occlusion as the real cause and without suitable medical treatment it may terminate in sudden death. Cardiac diseases may be responsible for psychoses.

**Hemiplegia.**—Patients may be ill with the symptom-complex of fever, dyspnea, cyanosis and cough for several weeks and suddenly develop a hemiplegia.

The paralysis may be the result of an acute coronary artery occlusion with the mural clot over the area of infarction forming a source of emboli. The absence of typical signs and symptoms of recent infarction of the myocardium may mislead one.

As to the correct diagnosis, until the hemiplegia occurs the possible etiologic factor may be overlooked.

**Pericarditis.**—The presence of the symptom-complex of fever with signs of a pericarditis in an elderly person always should make one suspect the presence of acute coronary artery occlusion being the underlying cause. The symptoms and signs may be typical in character and if the infarction involves the diaphragmatic surface of the heart the pain may be of the shoulder top type. Pain in the shoulder should not be treated

as a local process without considering the possibility of it being cardiac in origin.

**Hemoptysis.**—Not infrequently blood spitting accompanies cardiac lesions as the result of passive congestion of the lungs. Many of the infective processes, neoplasms and ulcerative conditions in the lungs are associated with dyspnea, chest pains and cough. The possibility of blood spitting being cardiac as well as pulmonary in origin calls for a very careful investigation of the heart which otherwise may result in incorrectly attributing the blood spitting to a lung lesion in the presence of congestive heart failure as the result of mitral valve damage.

The pulmonary lesions when tuberculous in origin are commonly located at the apices of the lungs. Areas of bronchiectasis may be found in any location in the lungs but not infrequently they are located at the bases, the distribution of the lesion being similar to those found in congestive heart failure.

Hemoptysis in the presence of a well-defined presystolic murmur and thrill in the mitral area practically excludes active pulmonary tuberculosis.

**Ascites with a Heart Murmur Present.**—The presence of ascites and valvular lesions of the heart are not necessarily the result of congestive heart failure. A young married woman, twenty-four years of age, noticed her abdomen gradually increasing in size. She consulted a physician who, upon examination, found her lungs clear and resonant throughout, the area of cardiac dulness was normal in outline and a presystolic thrill and murmur were present in the mitral area. The heart sounds occurred regularly and were of good quality. The liver could not be definitely outlined due to the presence of considerable amount of ascites. Slight pretibial edema was present. The blood pressure was 120/80, temperature 99.6° F., the respirations 26 per minute and the radial pulse 76 per minute. The patient was more comfortable lying flat on her back than sitting up. This observation with the normal lungs, heart rate and rhythm, with the presence of fever, by a process of elimination it was thought that the cause of the ascites and other signs and symptoms would be found in the abdomen. A small central incision under local anesthesia was made by a

surgeon, relieved the ascites and revealed the presence of widespread miliary tuberculosis of the peritoneum. With proper convalescence obtained for the patient her health was restored and she has enjoyed excellent health with the mitral lesion present and well compensated for, since 1921.

**Pulmonary Embolism.**—The slowing of the circulation in patients following long confinement to bed, postoperatively, in the treatment of fractures of the neck of femur or vertebrae and in chronic illness, may result in phlebitis occurring in previously varicose veins or in apparently normal veins. From these inflamed veins oftentimes clots are liberated and act as emboli passing through the right heart into the pulmonary artery and its branches. If the clot is of sufficient size death may occur immediately. At other times clots smaller in size, not sufficient in size to occlude the larger branches of the pulmonary artery, may lodge in the substernal region. The symptoms of shock with cyanosis and substernal pain make up this clinical picture. The symptomatology and signs may thus be very similar, early in the course of pulmonary embolism and acute coronary artery occlusion, but within twenty-four hours in the pulmonary embolism, if the patient survives, cough, expectoration, usually frothy and blood-tinged, occurs with continued degree of cyanosis and distention of the veins of the neck.

Electrocardiographic changes of myocardial weakness are present in both conditions but typical electrocardiographic findings are never present in pulmonary embolism, important early in the making of the correct diagnosis of coronary thrombosis.

**Paroxysmal Attacks of Pain in One or Both Arms.**—Neuritis-like pains in the left arm or both arms not necessarily referred from the substernal or precordial region. The referred pain experienced in the left arm only, the right arm only, or to both arms is so well known in association with an attack of angina pectoris or acute coronary artery occlusion as to require little comment.

The occurrence of this pain in both arms severe enough to awaken the patient from his sleep during the night with all symptoms of shock present, and requiring two hypodermic injections of morphine sulfate  $\frac{1}{4}$  grain at half-hour intervals

to afford relief, subsequently was proved to be due to an attack of acute coronary artery occlusion. Substernal distress was not severe enough to attract attention, nevertheless the diagnosis of acute coronary occlusion could have been readily overlooked but for serial electrocardiographic examinations. Although many instances of paroxysms of pain in the arms are not severe enough to produce shock with or without substernal distress and dyspnea, its presence in an individual more than forty years of age should be regarded as suspicious (possibly associated with coronary artery disease) until excluded by clinical observation and electrocardiographic examination.

**Convulsions and Temporary Loss of Consciousness.—**

Numerous instances of generalized convulsive seizures may occur in patients and be incorrectly diagnosed as to the etiology. These attacks may have been reported to a physician without the latter having had an opportunity actually to observe them. A diagnosis of epilepsy frequently has been made because the examination of the heart between attacks proved normal. An opportunity to observe the patient during an attack or an electrocardiographic study at that time may have revealed ventricular standstill, a prolonged PR interval, complete heart block or the special manifestation of heart block described as Adams-Stokes syndrome. Unless the physician has observed the attack and noted the condition of the circulation during the convulsion he is not warranted in making a final diagnosis of epilepsy. It is important to exclude every form of heart block with its resulting anoxemia by an electrocardiographic study before an etiologic diagnosis is made of any convulsive seizure or loss of consciousness.

Acute indigestion has been a term that has frequently masked underlying cardiac pathology. Considerable attention has been directed to the differential diagnosis between acute coronary occlusion and an acute surgical or medical condition in the abdomen. Ruptured peptic ulcer, gangrenous gallbladder or gallstones or renal colic, acute pancreatitis, acute appendicitis, acute lead poisoning, crisis of locomotor ataxia have been incorrectly diagnosed when the subsequent course of events proved the condition to be due to acute coronary occlusion.

Of importance is a previous history of similar attacks of

heart pain associated with various degrees of shock, an ashen gray color of the skin rather than pallor. In coronary occlusion the distress is usually beneath the sternum and in conditions arising in the abdomen the location of the distress is lower, even though in the epigastrium. Epigastric pain is not referred to the arms such as may be pain cardiac in origin.

**Subacute Bacterial Endocarditis.**—The very first symptom or physical sign resulting eventually in the diagnosis of subacute bacterial endocarditis may be an embolic phenomenon, such as in central retinal artery causing partial blindness, in the brain causing interference of the function centrally controlled in the area in which the embolism lodged. The pain over the splenic area may be traced to an embolism lodging in the spleen. The subacute arthritis may be the outstanding symptom of a subsequently recognized subacute bacterial endocarditis.

The findings upon examination of the urine of the presence of blood, albumin and casts may be discovered to be due ultimately to emboli lodging in the kidney from subacute bacterial endocarditis.

Fever-free stages as well as bacteria-free periods in the course of subacute bacterial endocarditis may temporarily delay the recognition of the presence of subacute bacterial endocarditis. The fact that this may occur should be of assistance in recognizing heart conditions, which otherwise can readily be missed.





## CLINIC OF DRS. JOHN H. STOKES AND LEONARD E. ANDERSON

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### THE DIAGNOSIS AND TREATMENT OF SYPHILITIC AORTITIS

THE best work in the field of syphilitic cardiovascular disease is done by the combined effort of cardiologists and syphilologists, rather than by either alone. The average practitioner, despite his inevitable and constant contact with the field of syphilis, flounders helplessly in the morass of technic and technicalities which the field of cardiovascular syphilis of necessity involves. The internist, hyperacute toward one or another aspect of the confusion border line, has been shown repeatedly by autopsy evidence<sup>1</sup> to have perished ignominiously between the diagnostic hay-bales of rheumatic aortic disease and syphilitic aortic disease. It would therefore be both unseemly and indiscreet for us not to credential ourselves in presenting this subject by reference to F. A. Willius and to C. G. Wolferth, who though they have not directly participated in the present discussion, have contributed at least alternate vertebrae in its backbone by supplying the fundamental expert knowledge of the pathologic physiology of the heart and aorta, and the physical diagnostic proficiency necessary to the weighing of the difficult questions which so constantly arise in the individual case. The roentgenology of the field is now sufficiently at the command of the cardiologist to make him a preferred referee for this part of individual case study; for the cardiologist's knowledge of the functional behavior of

the aorta, as depicted in the movements of the shadow, is at least fully as important as the mere mensural estimation of the shadow itself.

The problem of uncomplicated syphilitic aortitis, if it is to be recognized in the uncomplicated stage, is as difficult as it is critical. Too much emphasis cannot be placed on the statement that when a regurgitant aortic lesion, a hugely dilated heart, or a pulsating aneurysm is identified, somebody has fallen down on his job. For that reason, and because it is so fundamentally important that we drill ourselves constantly in the preventive outlook toward syphilitic cardiovascular disease, little is said in this presentation about the treatment of advanced and consequential syphilitic lesions of the heart and aorta. They constitute, we hope, the medicine of a passing, rather than a future generation.

A discussion of diagnosis and treatment in this field needs a minimal statistical background. It can be drawn almost entirely from two sources, with a third we hope to be added in the not-far-distant future. Bruusgaard<sup>2</sup> has, subject to certain inevitable limitations of material and method, portrayed quite clearly the biologic course of untreated syphilis with respect to the cardiovascular system in man. This form of involvement was not recognizable in untreated living patients within the three- to ten-year observation period, dating from onset of infection; appeared in only 1.5 per cent in the ten- to twenty-year group; sprang into recognition to the extent of 10 per cent in the twenty- to thirty-year group, and 12.5 per cent in the thirty- to forty-year group. Bruusgaard's methods, painstaking though they were, could not avail themselves fully of criteria of diagnosis which recent work by roentgenologists, cardiologists, internists and syphilologists has tended to emphasize. Granting to our newer material a reasonable though not as yet exactly determined validity, it appears, using the figures of the Cooperative Clinical Group<sup>3</sup> embracing 907 American patients receiving any and every form of treatment used by the investigators, that from 1916 to 1931, 0.7 per cent developed outright cardiovascular syphilis in the three- to ten-year period after infection; while 1.3 per cent developed a suspicious sign in the form of dilated aorta. In the ten- to twenty-year period 5.8 per cent of the patients

developed definite aortitis, and 4.6 per cent additional were open to suspicion. The difference between 10.4 in the Co-operative Clinical Group series and Bruusgaard's 1.5 per cent of aortic change or involvement represents possibly, though improbably, an advance in time of onset of syphilitic aortic disease under modern conditions of treatment. Far more probably, however, it represents the effect of employing for diagnosis physical and roentgenologic criteria which Bruusgaard did not use. Thus, despite Langer's<sup>4</sup> debatable contention of premature onset and the unsettled question as to whether our present criteria for early diagnosis genuinely represent the onset of syphilitic as distinguished from other forms of aortitis, we find ourselves obliged to use, for lack of anything better at the moment, a group of diagnostic symptoms and signs presently to be given that may prove, within the next several years, to have been the hotly controversial, rather than the coldly rational end of the diagnostic poker. Such a contingency we must accept with what grace and humility we can.

**The Pathologic Physiology of Syphilitic Aortic Disease.**—One is materially assisted toward an understanding both of the possibilities and the perplexities of diagnosis in the preventive period of syphilitic great vessel disease by an informal review of the pathology. There are a number of reasons for describing the syphilitic involvement of the aorta as a periaortitis and mesaortitis, the former as the probable initial phase.<sup>5, 6</sup> The more closely one studies roentgenologically and symptomatically the phenomena associated with therapeutic testing and clinical improvement in aortic syphilis with relief of symptoms accompanied by paradoxical increase of signs, the more is one led toward the belief that an inflammatory process in the mediastinal tissue around the aorta, quite as much as one within its wall, is essential to the explanation of much of the symptomatology and diagnostic signs.

The inflammatory changes in and about the aorta achieve their importance not only through their effect as such on the vessel wall, but through their location with respect to the heart.<sup>7</sup> The nearer the infiltrative process is to the aortic ring, the graver is the situation of the patient and the more certain is the development of regurgitation and of myocardial, by way of coronary, injury in the individual case. On the other

hand, the higher up the ascending portion of the aorta or the arch itself is involved, the more probable is the development of aneurysmal change through the effect of an intact aortic valve in maintaining diastolic pressure against a weakened vessel wall.<sup>6</sup> Thus it comes about that disease of the root of the aorta is in general of graver prognosis, granted an approximately equal date of recognition, than is disease of the upper ascending or arciform portion of the aorta. In general aneurysm, reasonably early discovered, is not incompatible with long and effective life. Disease of the bulb, however, with its involvement of valve cusps and coronary orifices, has a profound element of unpredictability and may, despite every therapeutic precaution, be found to eventuate in serious structural damage followed by marked limitation of working capacity and an easy transition into dilatation, breach of compensation and myocardial damage.

The roentgenology of early aortic disease, whether arteriosclerotic, rheumatic or syphilitic, owes much of its differential interpretation to the foregoing considerations. The increase in density of the aortic shadow can be recognized in both arteriosclerosis and in syphilitic aortitis. The age factor seems frequently to be invoked to distinguish the two. Apparently the arteriosclerotic type of change, with its tendency to calcification, less likely to occur in the syphilitic aorta,<sup>8</sup> leads to a wider, denser but more rigid tube than does the syphilitic inflammatory infiltrate with the weakened fibrotic wall to which it gives rise. Dilatation, with increased pulsation, together with an increase in density out of proportion to the patient's arteriosclerotic age expectancy, suggests, therefore, though it does not alone establish, a syphilitic type of pathologic process.<sup>9, 10, 11</sup> This we take to be the gist of the discussions which have marked consultation reports of cardiologists who personally examine with the fluoroscope the aortas of patients we have referred to them with the syphilitic differential problem in mind.

As in the roentgenology, so in the physical diagnosis; the pathologic physiology of aortitis, syphilitic or otherwise, makes rational the critical findings on physical examination which act as suspicion arousers and guides to ultimate diagnosis. Again, the higher in the ascending aorta the involvement reaches its

maximum, the fewer will be the early symptoms of which the patient complains. The symptomatology of early syphilitic aortitis is more apt to be symptomatology of the bulb. The sense of precordial stress, anginoid pain, actual anginal seizures, dyspneic storms, especially nocturnal, and the signs of failing heart, are in the main expressions or sequelae of bulbar aortic disease. Aneurysms present, in place of the symptoms and signs of cardiac embarrassment, the rather late-appearing earmarks of localized pressure—pain and the malfunction of special structures within the thorax. It is not suggested that the two processes are mutually exclusive, but in the main it is probably true that disease of the bulb with the breakdown of the valve is what saves the patient from aneurysm, only to bring him to an earlier death by the circulatory load thrown back upon an impaired heart.

The physical signs of aortitis and especially of syphilitic aortitis are easier to remember if one keeps the pathologic physiology in mind. Accentuation of the aortic second sound, as compared with the pulmonic, and a definite tonal change in its quality, is perhaps also expressive not of damage to the valve so much as change in the vessel wall, both in rigidity and texture, as in the case of the murmur according to experiments such as those of Reid.<sup>12</sup> Just what it is that makes the difference between the flat accentuation of the aortic second sound in arteriosclerosis, as distinguished from the hollow, drumlike tambour quality of the aortic second sound in syphilitic aortitis, pathologic physiology and autopsy observation do not as yet disclose. The question as to whether the clinical differentiation of these two tonal qualities rests on valid observation, no mere syphilologist can undertake to answer, but the consensus of cardiologic opinion concerned with syphilitic aortitis is that the tambour or drumlike change in quality has definite significance for syphilitic origin.

When it comes to the interpretation of murmurs, as distinguished from tonal quality, one enters a far less clearly illumined field. The chronologically initial systolic aortic murmur representing changes in valve or wall is indeed of most uncertain etiologic significance. Among the murmurs at the base of the heart it may all too easily, if taken alone, lead to serious diagnostic misinterpretation. That it can be a product

of arteriosclerotic change is undeniable. That it can equally well be produced by syphilis is equally undeniable. The stand apparently taken by many practicing physicians that no interpretation can be placed on such a murmur until it is accompanied by the diastolic murmur of regurgitation or by an Austin-Flint is, however, pressing the issue to the point where preventive considerations are forced to yield entirely to an academic diagnostic dispute. If one is to wait for diagnosis until regurgitation develops in a syphilitic aortitis, he has waited too long.

The weighing of the arteriosclerotic against the syphilitic factor in the interpretation of an aortic systolic murmur is not unlike the weighing of density and pulsation changes under the fluoroscope. Age factors, the general arterial tension and state, the tonal quality of the second aortic sound, variations produced by position, especially intensification on leaning forward, and above all the recurrence, time after time in physical examination, of essentially the same group of signs, would seem to us to have more importance in the diagnostic evaluation than the mere systolic timing of the murmur as such.

All interpretations of early signs of syphilitic aortic disease involve an appraisal of concomitant and collateral manifestations in the patient.<sup>13</sup> Thus again youth, for example, when accompanied by evidence of premature cerebral vascular disease for which there appears to be no familial and no essential hypertensive basis, increases the presumption of syphilis. Familiarity with the various clinical pictures of neurosyphilis and a pushing of the routine medical work-up of a doubtful case to the point of examining the spinal fluid, may not infrequently assist in attaching the aortic picture by inference directly to a syphilitic etiology. On the other hand it is quite as necessary to be familiar with collateral arteriosclerotic manifestations in the nervous system. It is important, too, to realize that time is not the only thing which brings arteriosclerosis as distinguished from active syphilitic inflammatory disease of the vessels into operation in a given case. Arteriosclerosis is possible in comparatively young persons and arteriosclerotic change is a reasonably expected, though uncertainly frequent, accompaniment of syphilitic as it is of many chronic infective processes. The gradual development, therefore, of

hypertension in a younger individual, particularly a rise in his diastolic pressure, when one knows that he has had syphilis. creates a double rather than a single or solely arteriosclerotic anxiety in his behalf. On the other hand, the appearance in the third and fourth decades of clear-cut evidence of cerebral arteriosclerosis, for example, only throws a strong presumption toward arteriosclerosis as the explanation of aortic signs. It does not establish it absolutely nor absolutely eliminate syphilis.

The problem of acute rheumatic fever as a factor in aortic inflammatory disease is far from evaluated. T. B. Mallory's<sup>5</sup> exposition of the characteristic pathologic changes in the aortic valve cusps of syphilis, and his insistence that they are impossible in rheumatic endocarditis with stenosis, does not take us quite far enough clinically to throw the rheumatic fever factor out merely on the demonstration of aortic regurgitation. But as syphilologists we have long taken and still do take the stand that given an aortic lesion in a patient, who, though seronegative on the blood at the time of examination, and with a history suggesting rheumatic fever, has a fair presumptive background for a syphilitic infection, presumptive acceptance of syphilis as an element in his aortic picture is not only justifiable but wise. As a practical issue the differentiation of rheumatic and syphilitic factors in an aortitis is, we believe, to be dealt with by the suitably performed therapeutic test<sup>14a</sup> rather than by the gesture of dismissal of the syphilitic possibility which it too often receives.

It sharpens the edge of early diagnosis again to recall the "too late" or consequential manifestations of uncomplicated syphilitic aortitis. They belong practically entirely in the domain of the slowly crippling, the irremediable and the fatal. Coronary disease has become almost inevitable in the patient whose aortic sinuses are once thoroughly scarred by an unidentified syphilitic process. Myocardial damage is inevitable in the large proportion of patients who have sustained coronary occlusion and fibrosis. Breach of compensation in the syphilitic patient is often of sudden onset and, as has been repeatedly pointed out, of grave prognostic significance.<sup>15</sup> So important is the first breach in the life expectancy of syphilitic aortic disease, that a wringing of hands is an entirely appropriate

gesture at the bedside of any puffing and panting patient whose syphilitic aortitis has, through disregard of early, even though sometimes controversial signs, been permitted to progress to actual breach. Aneurysm is the essentially stealthy member of the consequential quartet. Unless it is fortunately situated where it gives rise to a sharp and concrete pressure symptomatology it may progress to the point of hopelessness absolutely unrecognized.

We are now ready for the list of early diagnostic signs and symptoms which we quote, with some commentary of our own, from the Cooperative Clinical Group's<sup>15</sup> recent summary. The items are given in order of diagnostic importance.

- I. Teleroentgenographic and fluoroscopic evidence of aortic dilatation.
- II. A tympanitic, bell-like, tambour accentuation of the aortic second sound.
- III. A history of circulatory embarrassment.
- IV. Increased retromanubrial dulness.
- V. Progressive cardiac failure.
- VI. Substernal pain.
- VII. Paroxysmal dyspnea.

In the fluoroscopy the pulsation seems to rate at least as high as does the widening of the aorta. Increased density, while less specific, is often observed. Increased density, out of proportion to age and general arteriosclerotic signs, is suggestive but not diagnostic.

In the interpretation of the aortic second sound, in relation to hypertension and arteriosclerosis, the blood pressure should be taken more than once, and the patient's mind be set at rest regarding the procedure. The second examination, a day following that on which the first study is made, not infrequently reduces the importance of an apparent hypertension element very considerably. The rise in diastolic pressure, if maintained, is more significant than a high systolic pressure, and more suggestive of arteriosclerotic change than of uncomplicated syphilitic aortitis.

Inspection of every patient should include a keen glance at the "total person"—an appraisal of his mental and muscular tension, his facies as an indicator of his neurogenous substrate, his account of work, play, responsibility and problems as a



guide to his functional reactivity and neurocirculatory instability. Yet the disposition to rate a sign or situation as "functional" must be sharply controlled, especially in physician-patients. The cardiac impulse over the chest and above the clavicle with the patient fully at rest often is a revealing observational trifle. A wide heaving lift, even though of small excursion, to the left side of the thorax, a heavy wave running upward into the neck as the resting patient lies quietly before one, is a significant item, often adding great weight to otherwise slight murmurs and insignificant enlargement, in the estimation of circulatory organic as against functional disease.

Both in the interpretation of the foregoing findings, and in the interpretation of murmurs over the aortic area and the heart base, a previous knowledge of the patient's status is one of the most valuable aids. This is indeed one of the best reasons why a patient who acquires the disease should, if possible, early be placed under expert central supervisory direction and receive within the first five years the benefit of cardiologic consultation. To have become familiar with the sounds made by a given heart and great vessels over a period of years is one of the best assurances one can have that an interpretation of a pathologic state, if and when it develops, will be soundly and promptly made. In every case it is essential to approach the examination not casually, but searchingly and yet nonetheless with no disposition to read into essentially small or transient items a crucial and exaggerated significance.

The symptomatology of syphilitic cardiovascular disease, as given in the list is, in our estimation, late rather than early stuff. Diagnosis deferred until progressive cardiac failure appears; until substernal pain is clear-cut, not to say marked; and until the patient has developed the asthmatic nocturnal seizures designated as paroxysmal dyspnea is made so close to the border line of lasting damage and incapacity that prevention becomes an academic rather than a real issue.

**The Serologic Tests.**—The student of syphilitic cardiovascular disease two decades ago found himself hamstrung by the inadequacies and uncertain interpretations attaching to blood Wassermann tests. The expectancy of a positive result in aortic disease of syphilitic origin and the gradient of increasing sensitiveness combined with specificity which has marked

gesture at the bedside of any puffing and panting patient whose syphilitic aortitis has, through disregard of early, even though sometimes controversial signs, been permitted to progress to actual breach. Aneurysm is the essentially stealthy member of the consequential quartet. Unless it is fortunately situated where it gives rise to a sharp and concrete pressure symptomatology it may progress to the point of hopelessness absolutely unrecognized.

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the advance of serologic technic in syphilis is well represented by the following successive figures. In the Mayo Clinic series considered by one of us,<sup>14b</sup> no case of which postdates 1923, only 57.5 per cent showed strongly positive Wassermann reactions on the first test. By repetition and provocative procedures, this proportion was raised, however, to something short of 70 per cent. In Moore, Danglade and Reisinger's<sup>1</sup> survey of Johns Hopkins experience 75.3 per cent positives were obtained. Carter and Baker,<sup>10</sup> from the same institution, reported 92.6 per cent positives in their first 100 cases. Miller,<sup>17</sup> on our service at the University of Pennsylvania, obtained 81.8 per cent positive Kahn tests, and 84.8 per cent positive Kline tests. Prior to 1924, Elliott<sup>8</sup> had placed the margin of error of the negative blood Wassermann reaction in syphilitic vascular disease as high as 40 per cent. It has now dropped to 20 to 25 per cent and positive expectancy has ranged from 75 to 80 per cent. Since much syphilis recognized today has at one time or another in its life history received treatment for the disease, the Cooperative Clinical Group's<sup>15</sup> figures are useful. Of those patients with syphilis who had received no treatment or an unknown amount prior to recognition of the uncomplicated syphilitic aortitis, 83 per cent had a positive blood Wassermann reaction at the time the cardiovascular diagnosis was made. If more than 18 injections of an arsenical, with interim heavy metal, had been given prior to the detection of the uncomplicated syphilitic aortitis, the percentage of positive blood Wassermann reactions had dropped to 52.

While it will thus be apparent that serologic criteria in the diagnosis of syphilitic aortitis are of a variable and frequently uninterpretable uncertainty, the routine performance of serologic tests for syphilis as part of every medical examination will extend the range of our inquiry and recognition of superficially symptomless "latency." If therewith there can be developed an increase in the suspicion with which the syphilitic's heart and aorta are regarded and a willingness to treat, on that suspicion, the reasonable possibility of syphilis, we shall have the essentials of what one might call "late prevention."

The association of cardiovascular syphilis and neurosyphilis has been alluded to and has significant diagnostic

value. The Cooperative Clinical material,<sup>15</sup> which represents the latest expression on this matter, showed that 49 per cent of 191 cases of uncomplicated syphilitic aortitis receiving lumbar puncture within one month of the detection of the great vessel involvement showed unquestionable spinal fluid abnormality. It is not necessary, however, to press the matter to the point of lumbar puncture in every case. Close attention to pupils and reflexes, to the differentiation of pin-point and touch and of vibration sense, together with a carefully taken history, particularly of lightning pains, will often lead to a fairly convincing corroborative finding of syphilitic central nervous system involvement. In the presence of such signs, a negative blood and spinal fluid does not in itself exclude syphilis.

One more point in diagnostic technic in our opinion deserves emphasis. There is in diagnosis, as in therapeutics, a disposition to apply one's procedures seriatim rather than simultaneously to the evaluation of problems, too often allowing a case to stand under a negative finding, or to lapse when more persistence and completeness would have supported a judgment. In the field of cardiovascular syphilis we believe this to be a serious mistake. The appraisal of a patient for the diagnosis of syphilitic cardiovascular disease should not be made by serologic test or by physical examination alone, followed after a year or two by an electrocardiogram, and then subsequently by fluoroscopic or other study. The procedure in its entirety, and the syphilologic examination complete, coupled with a painstaking medical history, is not too much to employ in a consultative session, in the effort to detect and interpret the individual status with reference to syphilitic cardiovascular disease.

#### THE TREATMENT OF SYPHILITIC CARDIOVASCULAR DISEASE

**Prevention of Uncomplicated Syphilitic Aortitis.**—The last decade has brought several advances in knowledge of the treatment of syphilitic cardiovascular disease. The statistical evaluations of the American Cooperative Clinical Group and the United States Public Health Service, while they do not yet cover the twenty- to thirty- and thirty- to forty-year periods after infection, have established a strong presumption that the

use of adequate treatment for early syphilis with arsphenamine and bismuth has high preventive efficiency in controlling late syphilitic aortitis. The whole problem is of course complicated, as internists and cardiologists have not hesitated very properly to point out, by the small numbers of patients in the higher duration brackets of the material thus far assembled, and by the fact that it is still undecided what part if any of an aortitis in a given syphilitic patient is syphilitic and what part of it is aortitis of some other description, including even perhaps therapeutically induced damage by chronic heavy metal and arsenical intoxication.

We must accept for the moment these criticisms of present knowledge; and in doing so simply quote you in summary form the experience of the Cooperative Clinical Group.<sup>15</sup> Their terminology rates 20 arsphenamine injections, with the appropriate interim heavy metal treatment between arsenical courses, as adequate treatment. Of 318 patients with early syphilis, of whom 199 were observed from three to ten years, 41 from ten to twenty years, and 2 twenty years and over, only 5 patients developed uncomplicated syphilitic aortitis. Of 1226 patients receiving adequate regular treatment (equal to or in excess of the above described standard), only 2 developed uncomplicated syphilitic aortitis. The observation periods for this second group were, however, less than three years in 893, from three to ten years in 323, and from ten to twenty years in 10 cases.

Bruusgaard's<sup>2</sup> follow-up study showed 1 death per 100 with cardiovascular involvement in untreated syphilis, while the Cooperative Clinical Group series showed 1 death in 500 in the three- to ten-year period among its treated cases. Bruusgaard had 10 deaths per 100 with cardiovascular syphilis in the ten- to twenty-year untreated group, while the Cooperative Clinical Group had no deaths in 88 treated cases of the same duration.

Let us at least, while conceding the shortcomings of this statistical material, draw a certain amount of hope and encouragement from it. No one who has any considerable experience with syphilis through the life course of the infection is prepared to expect of any form of treatment an absolute control of syphilitic aortic disease. It does progress at times

in the face of negative serologic findings precisely as does vascular syphilis of the nervous system. It progresses, too, in spite of treatment which admittedly, however, is employed too late and after the process must have become well established and capable of crippling functional effect, even though stopped in its tracks at a given grade of damage. That large group of patients, likely to be larger in the future, who are recognized in latency by the findings of positive serologic tests for syphilis, as studied by Moore<sup>18</sup> for the Cooperative Clinical Group series, was found to present cardiovascular relapse or progression to some form of roentgenologically or clinically recognizable lesion in 1.6 per cent of cases.

Systematized preventive or "curative" treatment of early syphilis, intended to do away as far as possible with the manifestations of late syphilis, resolves itself at the present time into a choice between the two standard systems of treatment endorsed by the League of Nations Commission<sup>19</sup> which has had this problem under study for nearly a decade—the British-Danish intermittent and the American continuous alternating systems. With their universal adoption syphilologists at least are disposed to believe that an almost negligible residue of syphilis of the cardiovascular and nervous systems will remain to be dealt with in our patients' later lives. In fact the reexaminations after periods up to ten years of patients treated by either an ideal American sixty-five weeks' continuous or a twenty-one months' American type intermittent system, as currently in process of evaluation in this country, reduces all forms of progression of the disease, significant and nonsignificant, to 8 to 10 manifestations per 100 cases, including serologic relapse. Under ideal continuous treatment no cardiovascular complication has thus far appeared. Under ideal intermittent treatment, 0.7 per cent of patients developed cardiovascular progression and under irregular treatment 0.9 per cent.

The distinctive features of the American alternating continuous system of treatment for early syphilis are:

- (A) The complete absence of rest intervals, purposeful or otherwise, at least during the arsphenamine-heavy metal phase.
- (B) A duration or prolongation of treatment to a full sixty-five weeks—or, failing that, every effort to keep the treatment continuous for at least the first six to eight months.

(C) The administration of 32 adequate doses of an arsphenamine (or neoarsphenamine) intravenously (0.45 to 0.75 Gm. "914") with weekly intervals between injections in courses of not less than 8 injections for the first and 6 for the second, third, fourth and fifth courses. The arsenical courses alternate with courses of weekly intramuscular injections of not less than 0.2 Gm. bismuth salicylate or its insoluble equivalent to a total of 60 intramuscular injections. The earlier alternating bismuth courses may be of 4 to 6 injections each. Upon the completion of the arsenical phase of the treatment, the bismuth courses may be lengthened to 10 or 12 injections each, separated for the first time by complete rest intervals of eight to ten weeks, provided the spinal fluid has been negative before the first rest period is begun.

For the many patients who come to us in latency with only positive serologic tests to prove the existence of their infection, a technic of treatment for latency has been proposed on the basis of the Cooperative Clinical Group evaluation of this phase of the disease. It should be recalled that this system aims more at the prevention of future disability and the stopping of progression than it does at mere serologic reversal. This Cooperative Clinical Group<sup>18</sup> system for latency of more than four years' duration consists of 24 injections of an arsphenamine, given in 3 courses in alternation with heavy metal (preferably bismuth) without rest intervals until after the arsenical phase is completed. Subsequent prolongation of the heavy metal therapy varies somewhat with the individual factors, but in general this phase of the treatment should be prolonged (about one to two years) with rest periods of eight to ten weeks between bismuth courses of 10 to 12 injections after the arsphenamine phase is over. Yearly courses of bismuth in succeeding years up to three, five or even ten are commended.

**The Treatment of Recognized Syphilitic Aortitis.**—So much then for preventive treatment before the development of outspoken, clear-cut signs of syphilitic aortitis. Once these have developed we confront on the one hand inadequate and insufficient treatment for the syphilitic factor in the cardiovascular picture, and on the other, as Scylla to Charybdis, excessive and ill-judged treatment for syphilis at the expense of injury to the aorta and heart by therapeutic shock and



therapeutic paradox. In the last ten years it has been interesting to watch how the set-back of discovering that we were killing patients in the process of "curing" them of cardiovascular symptoms and signs, has gradually given way to a more hopeful reaction and a renewed boldness in the use of the arsenicals particularly in the treatment of uncomplicated syphilitic aortitis. Most of the damage done in the 1910's to 1920's by the brash and excessive use of the arsenicals arose from the fact that these drugs, with their excessively rapid healing effect, were used on advanced cases and cardiovascular wrecks rather than on patients in the earliest stages of aortic involvement. Under such undifferentiated treatment, therapeutic shock killed some patients with aneurysm within forty-eight hours after the first injection of a full dose of "606" or "914," and relieved other patients for a month or two of their anginal symptoms only to have them perish miserably of an uncompensated healing sclerosis of their syphilitically involved aortic bulbs and coronary orifices. Such unintended misuse of modern treatment for syphilis should now be an affair of the past. A safe approach to the treatment of syphilitic aortitis with the avoidance of therapeutic shock and paradox can be made today either by the preliminary use, over a period of weeks, but more often of months, of a heavy metal and iodide before the arsenical treatment is begun. A second method, long in use, consists of the employment from the outset of an exceedingly small but ascending dose of an arsenical or a combined arsenical and heavy metal (as in bismuth arsphenamine sulfonate) over a long period.

The question of selection of a heavy metal for preparatory treatment, with a choice between bismuth and mercury, cannot in our opinion be regarded as wholly settled. Bismuth is a faster-acting drug than is generally realized, and is enough like an arsphenamine in its action so that it is wiser to use very small and more frequent doses of a rapidly absorbed and rapidly eliminated salt, such as the water-soluble sodium bismuth tartrate, than it is to use the large doses of some of the insolubles applicable to the treatment of other phases of late syphilis. Even with such precaution one is occasionally seriously disturbed by evidences of early strain on compensation and threatened breach in patients who were ambulatory

and fully effective just before bismuth treatment was begun. Larger doses of bismuth are quite capable of producing the shocks and paradoxes of the larger doses of the arsphenamines, eventuating at times and quite unexpectedly in sudden death. For that reason, mercury in the form of the inunction or the succinimide given two or three times weekly by intramuscular injection still holds a legitimate and conservative place in the treatment of syphilitic cardiovascular disease. The earlier the aortitis; the higher in the vessel the involvement occurs; the more complete the absence of coronary symptoms; and the less the evidence of cardiac embarrassment, the stronger, more intense and more rapid can be the therapeutic approach. In fact the tolerance of uncomplicated syphilitic aortitis for the arsphenamines, when the disease is in its earliest stages, is such that the observations both of Moore, Danglade and Reisinger,<sup>1</sup> and of the Cooperative Clinical Group,<sup>15</sup> seem to justify the use of 0.45 Gm. neoarsphenamine as a maximum dose to be reached by the third or fourth injection of an ordinary 8- or even 10-injection series. It is to be stressed, however, that the administration of neoarsphenamine in cardiovascular syphilis must be so conducted that no reactions to the treatment are produced. Arsphenamine proper (606) should, in general, *not* be employed.

Should treatment be begun with an arsphenamine? It is notable that the Cooperative Clinical Group's recommendations still adhere to the conception of an introductory course or courses of heavy metal as a preparation. This, in our opinion, is particularly essential when aortitis has progressed to the appearance of a diastolic murmur; when an aneurysmal grade of aortic dilatation, and especially a small localized sac, is demonstrable by x-ray; when a differentiation between a tumor and a large aneurysm is to be made; when a large aneurysm is known to exist; when myocardial disease, as shown by the electrocardiogram, or coronary disease, as shown either by this means or by symptomatology, is present.

The selection of a form of preparatory treatment is not a matter of rule, but of individual case decision. Even in early uncomplicated aortitis and always in the presence of definite leakage the patient should, for a period of two months or more after treatment begins, reduce his activities or even submit

to rest in bed while the therapeutic shock adjustment takes place and healing and compensation for the defect are established. Getting in a hurry on the part of the doctor, and over-activity on the part of the patient, take especially heavy toll of what might otherwise be good results in this initial period. The prevention of shock and paradox of injurious grade is accomplished by an interplay between the activity of the drug, the amount of it administered per treatment, the interval between treatments, the resting of the patient, and the supporting of the circulatory machinery by such agents as digitalis. The gravity of the first breach in compensation for a patient with cardiovascular syphilis is, as we have said, now clearly recognized, and it is much wiser to be a bit exacting on the preventive side and slow on the therapeusis than to tax the patient to the point of even a mild decompensation. Within the skeleton of principles outlined, it is then possible to develop a satisfactory technic of dealing with the majority of cases. whether the mercurial inunction, minute doses of water-soluble bismuth (sodium bismuth tartrate), very small ascending doses of neoarsphenamine (25 mg. increment added to this as an initial dose), or bismuth arsphenamine sulfonate (bismarsen) in the same dosage is used. The courses are longer than in the more standard treatment of an uncomplicated early aortic case, the intervals between even the smallest doses of any of the last mentioned drugs seldom less than three or four days. *No attention should be paid to the failure to reverse blood serologic tests.* If and when possible, information should be obtained as to the spinal fluid and central nervous system findings. Reversing the dictum, more attention paid to the state of the cardiovascular mechanism, especially in patients in their late fifties and sixties, before any form of treatment for a neurosyphilis is undertaken, would forestall some serious and even fatal therapeutic decisions, especially in the use of fever therapy. While cardiovascular syphilis stands treatment better than, in the reaction again early paradoxical fatalities, we came to believe it would; and while it is now proved that neoarsphenamine materially betters results, caution and conservatism are still very much in order.

Even after years of observation, the action and use of iodide in cardiovascular syphilis are still a perplexity. Its slow effects

have been lost sight of too, in the spectacular action, for better or worse, of more modern drugs. Personally we have seen neither advantage from nor excuse for preference of one over another iodide, or the use of very large doses. Potassium iodide in 5- to 10-grain doses three times daily, two months on and two off, has been our most serviceable formula, continued in late cases over periods of years.

Is it possible statistically to maintain the worth of modern treatment in syphilitic aortic disease? With adequate treatment set, as before, at 20 properly graded arsphenamine or neoarsphenamine injections, and the appropriate heavy metal therapy, the Cooperative Clinical Group<sup>15</sup> material showed that the outlook of patients with uncomplicated syphilitic aortitis, followed for one year, had been improved, and the life span of those who died had been lengthened from an average of thirty-four to eighty-five months. Small arsenical dosage prolonged life twenty months more than the larger ones. Of patients adequately treated after the detection of their aortitis, 63 per cent were found to be living, symptom-free and arrested; while of those inadequately treated only 49 per cent were so found.

Perhaps a final word might be offered in explanation of a finding after treatment which sometimes does the doctor's cardiovascular mechanism more injury than it does the patient's. This is the so-called "paradoxical increase in signs" which may occur even with the bringing of the aortic syphilitic process to a standstill and the general functional improvement of the patient. This paradoxical effect manifests itself, for example, in the patient who has been recognized as having a syphilitic aortitis with a systolic aortic murmur, but no regurgitant diastolic murmur. Six months after adequate and carefully graded treatment for the aortitis has been administered, he is found to have not only his aortic systolic, but also a diastolic murmur, and perhaps some definite evidence of cardiac enlargement incident on the regurgitation. Is this patient worse or better as the result of the treatment he has received? Enough of these instances have now accumulated so that we believe it is safe to say from observation of them that they have simply exchanged a static disability for a progressive and threatening one. If they had not been treated they would ultimately have

gone on to a far more advanced grade of aortic damage than that made manifest in their healing sclerosis. The paradoxical effect is observable in a wide range of syphilitic aortic disease, and may take the form of the development of outright aneurysm upon a merely pulsating and somewhat widened aorta; the enlargement of an aneurysm beyond the size observed at the time treatment was begun; the development of aortic systolic as well as aortic regurgitant murmurs; the appearance of transient signs of decompensation in many patients with what appear to be very mild grades of aortic involvement due probably to temporary disturbance of the coronary circulation; and finally to the recognition in subsequent fluoroscopy of aortic dilatation and pulsation which, as in one of our most recent cases, surprised the cardiologist, who had expected an entirely different effect from properly conducted treatment.

We have presented this subject more in the form of an oration than a clinical demonstration because it has seemed to us that above all else statements of principle, even though some of them have only tentative quality and coloring, are more needed in this field than is a mere multiplication of case instances. Syphilitic cardiovascular disease has been far too well considered by the case, and far too little in the aggregate and by principle. As the weak spots in the frame of principles are more carefully studied (*vide* the differential field between syphilitic and other forms of aortitis), the general practitioner can expect a widening of his usefulness in the special treatment of late cardiovascular syphilis. In the field of prevention, however, he stands today as the holder of the strategic position. Once he has mastered the principles of effective treatment of early syphilis, the rôle of the cardiovascular specialist with respect to this particular disease will fade into obscurity.

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## CLINIC OF DR. JOSEPH B. VANDER VEER

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#### THE DIAGNOSIS AND TREATMENT OF ABNORMAL CARDIAC RATES AND RHYTHMS

DISTURBANCES in the rate and rhythm of the heart are frequent. Occurring in persons with normal hearts they may produce symptoms sufficient to cause alarm. With organic heart disease existing symptoms may be aggravated and the prognosis unfavorably altered. In other cases the onset of an arrhythmia is a sign of activity of myocardial disease or a warning signal denoting overtreatment. As in the whole of medicine, correct diagnosis is the foundation of good treatment.

The more widespread use of the electrocardiogram has led to a new interest and accuracy in the diagnosis of these conditions. Sir James Mackenzie said, "The eventual use of machines in diagnosis is to teach us how to do without them." It is rare that a patient with an arrhythmia or tachycardia cannot be correctly diagnosed and treated by clinical methods alone, if the physiology and clinical signs of these conditions are known to the observer. In this discussion emphasis will be placed on the clinical examination. A few electrocardiograms are included with the hope that even those unfamiliar with this method of examination may be given a mental picture of the physiologic changes which occur in these disturbances.

#### SINUS ARRHYTHMIA

This is one of the most common disturbances of cardiac rhythm and usually results from the vagus effect on the sino-auricular node, or pacemaker. It is most frequent in children and young adults. Its main importance lies in its differentiation from other arrhythmias. It is usually associated with

respiration and the condition can be accentuated (thus aiding in diagnosis) by having the patient breathe deeply and slowly. Once regarded with some importance it is now thought to be of little clinical significance and no treatment is indicated.

### PREMATURE BEATS

Premature beats, or extrasystoles as they are often called, are frequently seen in both normal and diseased hearts. Patients often consult a physician because of the symptoms produced. In other instances, often more important, frequent premature beats are present without the patient being aware of the arrhythmia. These ectopic contractions may arise from any portion of the heart muscle or conduction tissue. Occasionally the premature contraction is "interpolated" between two normal beats, a true "extrasystole." As a rule, however, the premature beat replaces the next ventricular contraction, the ventricular muscle being in the refractory stage when the regular stimulus reaches it. The pacemaker in the auricle continues the rhythm and the ventricles respond to the succeeding stimulus. This compensatory pause is characteristic of premature beats, though it may not be of complete length in the auricular type where the pacemaker is disturbed.

**Diagnosis.**—The diagnosis of premature beats is often suspected from the history, the patient complaining of a "flopping" or "turning over" sensation in the cardiac area. They are more apt to occur when the heart rate is slow, as after retiring or on arising in the morning. On auscultation of the heart the regular rhythm is broken by an audible premature beat, followed by a compensatory pause. The sounds of the premature contraction often vary slightly from the normal. Only one sound (the first) may be heard when the contraction is too weak to open the aortic valves, or there may be a "tumbling" quality to the cycle with three quick, distinct sounds. Coincident palpation of the pulse reveals no wave or one of diminished volume followed by a pause. Premature beats arising in the auricle or A. V. nodal tissues may produce a pulse wave as the stimulus reaching the ventricles follows the usual conduction path and the resultant contraction is a competent one. One of the most valuable signs of digitalis intoxication in a patient with normal rhythm is the appearance



of premature beats. If the drug is continued a coupling of premature beats may occur (*i. e.*, each normal contraction is followed by a premature one). A slow, regular pulse may be present—the premature contractions producing no pulse wave, and the condition inaccurately diagnosed as heart block. A coupling of the pulse is sometimes present, however, especially if the premature beats arise in the auricle. In these cases the second pulse wave is distinctly smaller than the first. Differentiation of this condition from the more rare true pulsus

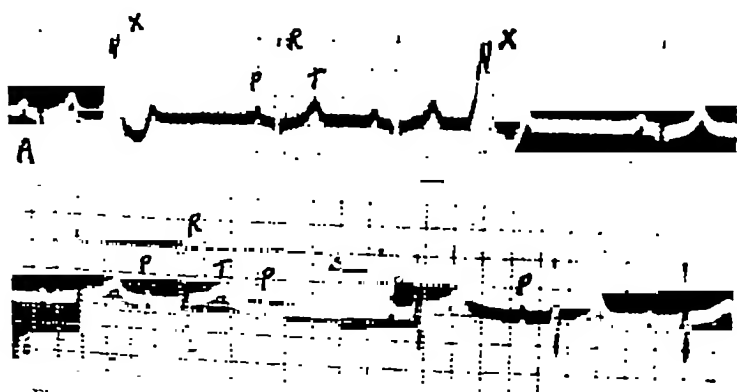


Fig. 55.—Electrocardiograms showing the difference between premature beats and partial heart block. *A*, Lead I, from a case with ventricular premature beats. Note the aberrant ventricular complexes produced by the premature beats (X) and the compensatory pause. *B*, Lead II, from a case of delayed auriculoventricular conduction with occasional failure of the stimulus to reach the ventricle. Note the prolonged P-R interval and the failure of ventricular contraction (X). These two conditions may give identical "dropped beats" in the pulse but coincident auscultation of the heart reveals the true diagnosis.

alternans is easily done clinically, for in the latter the pulse waves are equally spaced. Coupling with premature beats is most apt to occur in patients with severe myocardial damage. It should be stressed that in this type of patient (who often has the greatest need for the drug) the margin of safety between the therapeutic and toxic dose of digitalis is least. The appearance of this rhythm in a patient receiving digitalis is a signal for immediate cessation of the drug.

Frequent premature contractions from many foci, occurring

with an increased heart rate, may be most difficult to distinguish from auricular fibrillation. In both, irregularity in force and rhythm of the pulse with pulse deficit may be present. Frequent, careful examination of the patient will suffice to differentiate the two in most cases, though occasionally an electrocardiogram is essential.

Irregularity of the pulse from partial heart block may exactly resemble that seen with premature beats. If the heart sounds are well heard, however, the two conditions are easily classified, the premature beats being audible whereas the failure of the ventricle to contract in heart block leaves those intervals of the cardiac cycle without sound (Fig. 55).

**Treatment.**—In those patients in which no evidence of organic heart disease is found reassurance that the condition is not serious should be given. The etiologic factor may be a minor one and easily removed if located. The combination of fatigue, worry, and increased use of tobacco is a common cause. Foci of infection, especially apical abscesses of the teeth, are responsible for some cases. Improvement of the general health when secondary anemia and chronic infections are at fault, may prove beneficial. The time-honored use of strychnine and quinine is probably based on an increase in the cardiac rate and a decrease in cardiac irritability, though removal of the cause whenever possible is more desirable. In those patients with irritable hearts having frequent premature beats and periods of tachycardia the use of quinidine may be indicated (see paroxysmal tachycardia).

Infectious diseases, especially pneumonia, often show premature beats at some time during their course. Myocardial involvement by a toxic or infectious process is suggested but no special therapy is indicated in most cases.

In patients with organic heart disease the presence of frequent premature contractions, especially if the heart rate is elevated, suggests an active myocardial affection. Frequent auricular premature beats may be a forerunner of auricular fibrillation. When extrasystoles appear after coronary occlusion (acute myocardial infarction) it may be a warning that ventricular fibrillation is imminent. The use of quinidine sulfate, 3 grains every four hours, when awake, is rational

therapy to reduce the irritability of the ventricular musculature and lessen the possibility of this fatal rhythm.

The appearance of premature beats during digitalization or in patients on a maintenance dose of digitalis is a sign to proceed cautiously. If they become frequent or a coupled rhythm is noted the drug should be stopped *at once*, even though nausea and vomiting or other symptoms of intoxication are absent. Premature beats, *per se*, however, are not a contraindication for digitalis. Occurring in a patient with heart disease who has received none of the drug, digitalis should be given if there are signs of myocardial insufficiency. In these cases the irregularity may lessen or disappear with digitalization. The same may be said of nausea and vomiting in patients who have received but small doses of digitalis. If these symptoms are due to passive congestion of the liver and stomach the indication is for more, rather than less digitalis.

#### PAROXYSMAL TACHYCARDIA

Paroxysmal tachycardia is characterized by the abrupt onset of a rapid, regular heart action persisting for a period of a few seconds to a few days and terminating abruptly. The condition has been likened to a rapid succession of premature beats and similarly, the focus of irritability may be located in the auricle, A. V. nodal tissues or the ventricle. It occurs frequently in hearts with no evidence of disease and in these cases is seldom serious. When an attack persists for several hours in a patient with organic heart disease signs of decompensation may appear. The type of paroxysmal tachycardia usually seen originates in the auricle or A. V. nodal tissues and has a rate of 160 to 220 per minute. Even more rapid rates are occasionally seen. The more serious, but uncommon, ventricular tachycardia is seen after myocardial infarction and with overdosage of digitalis. The rate is usually less rapid and often a slight irregularity in the rhythm is present. Ventricular fibrillation is to be feared in these cases.

**Diagnosis.**—The diagnosis of paroxysmal tachycardia is often suspected from the history. The abruptness of onset and termination are characteristic and previous similar attacks have usually been experienced (Fig. 56). Palpitation is nearly always present. Shortness of breath, weakness, and dizziness

are common. Auscultation of the heart reveals a rapid regular rhythm. No pulse deficit is present and the volume of the pulse is constant, though small. Accurate determination of

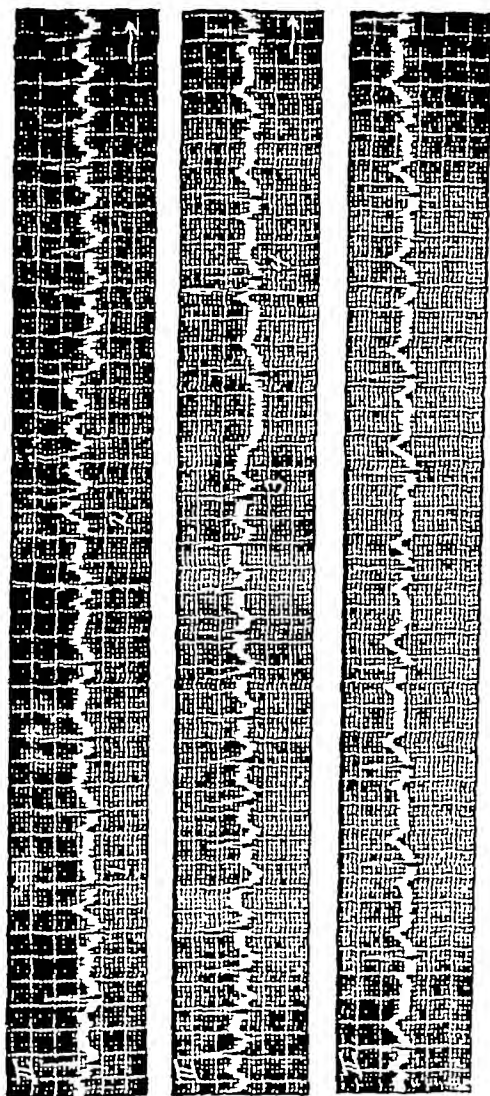


Fig. 56—Electrocardiogram of a complete attack of paroxysmal tachycardia (continuous record of Lead II). Normal sinus rhythm is present at the first of the record with an isolated premature beat shown at 1. The abrupt onset of the tachycardia is evident at 2. The rate is 172 per minute and the attack lasts 9.2 seconds. The abrupt cessation of the attack occurs at 3. Normal rhythm is resumed at 4 with a rate of 78 per minute. The focus of origin of the premature beat and tachycardia is in the auriculo-ventricular bundle (His). The "paroxysmal" character of the condition is well shown.

the pulse rate may be difficult but the correct rate of the tachycardia can usually be determined by the stethoscope. This condition must be differentiated from *auricular flutter* and

rapid *auricular fibrillation*. Though these latter rhythms may occasionally be paroxysmal in type they are usually persistent and more apt to occur with organic heart disease. The ventricular rate in flutter is usually at or below 160 per minute whereas that of tachycardia is commonly above this rate. Very rapid pulse waves may be seen in the neck veins (due to auricular contractions) in some cases of auricular flutter. Pressure over the carotid sinus area may produce slowing of the arterial pulse (during the time of pressure) in flutter. Very rapid auricular fibrillation may give the impression of a regular heart rate to auscultation, especially if one does not listen specifically for slight arrhythmia. Coincident palpation of the pulse, however, reveals irregularity in force and rhythm with a marked pulse deficit. This clinical observation differentiates fibrillation from tachycardia.

Ventricular tachycardia should be suspected when a patient with severe heart disease who is receiving digitalis develops a rapid heart rate. It is also apt to occur following coronary thrombosis. The final differentiation from auricular and nodal tachycardia must be made by the electrocardiogram.

**Treatment.**—Patients with frequent attacks of paroxysmal tachycardia often discover various methods of terminating the attacks. Holding the breath, taking a deep inspiration and “bearing down,” a drink of ice water, the induction of vomiting by an emetic or putting the finger down the throat, pressure on the neck or eyeballs and other procedures may prove efficacious in the individual case. Probably the most frequently successful method of terminating an attack is by pressure on the right carotid sinus. The patient should be flat or semi-recumbent so the neck is relaxed. The first three fingers are rolled medially over the sternocleidomastoid muscle and the carotid artery palpated just below the angle of the jaw. Firm continuous pressure is made so as to compress the artery against the underlying structures. This is continued for ten to twenty seconds and it may be necessary to exert considerable pressure. If unsuccessful, the measure should be repeated in slightly different areas.

When the tachycardia persists the patient should be kept quiet and in a comfortable position, usually recumbent. An ice-bag should be placed on the precordium and a sedative

given. If much discomfort is present morphine hypodermically is indicated. The attacks usually terminate in a few hours and the patient quickly returns to his usual health. If organic heart disease is present symptoms of cardiac failure may soon appear and more drastic measures are indicated. Quinidine sulfate, 3 to 6 grains, should be given every two to three hours for several doses. The use of acetyl-beta-methylcholine chloride (mecholyl) may prove successful when other measures fail. This drug, a powerful parasympathetic stimulator, is given hypodermically in doses of 15 to 30 mgm. Flushing of the skin, increased peristalsis and even bronchial spasm quickly occur and the tachycardia may terminate within two or three minutes. Pressure on the neck may again be tried if the drug does not act favorably alone. Because of possible severe reactions a hypodermic of atropine sulfate,  $\frac{1}{75}$  grain, should be immediately available and given at once if untoward symptoms are noted.

If ventricular tachycardia is suspected in patients receiving digitalis the drug should be stopped at once and quinidine started. Occurring after coronary occlusion it is an ominous sign but treatment may be successful and quinidine is probably the drug of choice. Rarely, short attacks of paroxysmal tachycardia recur with such frequency as to be disabling. In these patients improvement of the general health and removal of foci of infection are important. Quinidine sulfate may prove of value in reducing the number of attacks and should be tried in doses of 3 to 6 grains, three or four times daily. The drug can be continued for long periods of time though occasionally diarrhea or a troublesome dermatitis may occur and limit its use.

#### AURICULAR FLUTTER

This important but uncommon condition is usually associated with heart disease and may persist for weeks or months if untreated. It is most often seen with arteriosclerotic heart disease but occurs with rheumatic heart disease and occasionally with thyrotoxicosis. The process in the auricles is characterized by a regular circus movement stimulating the auricles to rapid contraction, usually at a rate of 260 to 320 per minute. A 2:1 auriculoventricular heart block is commonly present so the ventricular rate observed is from 130 to 160 per

minute. The patient is frequently unaware of the increased heart rate and may be brought to the physician by the symptoms of cardiac insufficiency.

**Diagnosis.**—Auricular flutter should be thought of in any patient with a heart rate of 120 to 160 per minute, which persists for several days or weeks with little variation in rate. If the condition is considered the diagnosis can usually be proved clinically. Careful inspection of the neck veins may reveal rapid venous pulse waves, caused by the auricular activity. This observation may be facilitated by having the patient in the prone position so as to distend the veins. Pressure on the carotid sinus area, as described under paroxysmal tachycardia, will often produce slowing of the ventricle rate in auricular flutter. The original rapid rate is quickly resumed on release of the pressure. This test may be of value in differentiating flutter from paroxysmal tachycardia. In the latter case there is no slowing of the heart rate—the attack being either abruptly terminated or no change in rate occurs. Occasionally, when a 3:1 or 4:1 auriculoventricular heart block is present in auricular flutter the slow, regular ventricular rate will be regarded as normal sinus rhythm. With a mixed auriculoventricular block and a rapid, irregular ventricular rate, auricular flutter is nearly identical with auricular fibrillation clinically and usually will be regarded as such. As the treatment is identical this error is of no practical importance. The treatment of auricular flutter will be discussed with that of auricular fibrillation.

#### AURICULAR FIBRILLATION

This condition is the most frequent, persistent arrhythmia and easily the most important of the disturbances of cardiac rhythm. It is closely related to auricular flutter. The circus movement in auricular fibrillation is more rapid, however, being in the neighborhood of 500 per minute, and follows an irregular course. Coordinated contractions of the auricles do not occur as in flutter or normal rhythm and they have aptly been described as being in a state of "tremulous diastole." This inactivity of the auricles impairs ventricular filling and favors thrombus formation in the appendages. The ventricles are bombarded by the numerous small stimuli from the muscle fiber contractions of the auricles. The bundle of His, because

of its refractory period, conducts only a portion of these stimuli. The resultant ventricular response is usually a rapid rate with a very irregular rhythm. When some degree of heart block is present from disease or as occurs with digitalis therapy, the ventricular rate will be slower, at times even below that usually seen with normal sinus rhythm. The auricular phenomena in these cases, however, remain unchanged.

Rarely, auricular fibrillation occurs in short paroxysmal attacks in individuals with no demonstrable heart disease. These attacks are apt to follow indiscretions in food and drink, severe fatigue, or overexertion. Persisting from a few minutes to a few hours, they usually subside spontaneously. During the course of severe infections, especially pneumonia, in toxic states from various causes, and occasionally postoperatively this rhythm may occur and persist from a few hours to a few days.

The development of auricular fibrillation in a patient with organic heart disease may at once change the prognosis and treatment. If the ventricular rate is rapid cardiac decompensation is to be expected, the rapidity of development depending on the myocardial reserve. Embolism is not infrequent in established auricular fibrillation, being more common in those patients with mitral stenosis, which augments the auricular stasis already present and favors auricular thrombus formation.

Etiologically, most cases of auricular fibrillation are associated with rheumatic heart disease or arteriosclerotic heart disease. Thyrotoxicosis is a much less frequent, but important cause. Most cases below forty years of age are in patients with mitral stenosis. In the older patients coronary sclerosis with or without hypertension is the usual cause. Hypertensive heart disease in adults of the younger age groups is seldom associated with the condition and it is practically never seen in syphilitic heart disease.

**Diagnosis.**—Characteristically, auricular fibrillation has a rapid, totally irregular ventricular rhythm with a pulse deficit. The pulse is irregular in force and rhythm. Any patient with a heart rate continuously above 120 per minute and totally irregular in rhythm can be safely regarded as fibrillating. As the heart rate increases the pulse rate becomes relatively less, due to the greater pulse deficit. With very rapid rates the



heart may sound nearly regular to auscultation but coincident palpation of the pulse shows that many of the contractions do not produce a pulse at the wrist. This dropping of pulse beats (pulse deficit) differentiates the condition from *paroxysmal tachycardia*. Taking the blood pressure may also aid in the diagnosis of auricular fibrillation. No regular upper level of systolic pressure is found, but rather a medley of beats is heard at different systolic levels. If the ventricular rate is inherently slow (partial heart block being present) or controlled by digitalis therapy, the rhythm may be remarkably regular. With a rate of about 70 per minute, or less, it is easily mistaken for *sinus arrhythmia*, occasional *premature beats* or even *normal sinus rhythm*. The error is not of great importance if the rate is fundamentally slow as no specific treatment is usually necessary. However, the mistake of stopping digitalis in well regulated cases because the "rhythm seems nearly regular" should be carefully avoided. Due to the prolonged effect of digitalis the ventricular rate shows little change for two or three weeks and the patient and physician are given a sense of false security. After this period the rate will rise rapidly to the original level and the improvement in cardiac reserve which has been gradually won may be quickly lost.

**Treatment.**—Congestive heart failure is often present in patients with auricular fibrillation or auricular flutter. Complete bed rest, light diet, free movement of the bowels, limitation of fluid intake to 1200 or 1500 cc., and the securing of sleep by morphine hypodermically, are all important measures in these cases.

Digitalis is the important drug in the treatment of these two conditions. It is indicated in practically all cases in which the ventricular rate is more rapid than normal, whether or not heart failure is present. The fundamentals of digitalis therapy can be stated as follows:

1. The *preparation of choice* in nearly all cases is powdered digitalis leaves in capsule or pill form.
- 2 The *digitalizing dose* is *sufficient* of the drug to produce beneficial effects with a minimum of toxic symptoms.
- 3 The *maintenance dose* of digitalis is that amount which gives the maximum cardiac efficiency; usually given daily, and often continued for life.

At the present time there is practically unanimity of opinion among cardiologists that the most efficient form of the drug is the whole digitalis leaf. It is more stable than the tincture and the dose prescribed is less apt to be altered by the druggist or patient. There are many excellent preparations of the glucosides of digitalis available at the present time. There is no proof, however, that these products have *any* advantage over a well standardized preparation of digitalis leaves, and the cost to the patient is usually greater. The psychic effect of a different appearing tablet may occasionally be a factor to be considered in patients who have been nauseated by digitalis or those convinced they are "sensitive" to the drug.

The amount of digitalis necessary for digitalization varies greatly in different patients. I am not convinced there is any advantage in prescribing digitalis according to the weight of the patient. While this may be a safe dose in most cases, it is not invariably so, and the best interests of the patient will be served if the drug is given in divided doses, three or four times daily, continuing this until improvement or toxic effects are manifest. Close observation is important, for in a patient with a badly damaged heart *signs* of toxicity may appear before symptoms, and either or both may occur before beneficial effects. In a moderately ill patient with rapid auricular fibrillation an initial dose of 6 to 9 grains should be given. The drug is then started in doses of  $1\frac{1}{2}$  grains (1 cat unit) three or four times daily. Careful observation should be made of the patient at least once daily, particularly noting the *heart rate*. As the ventricular rate slows the pulse deficit lessens and the quality of the pulse improves. The drug is given until the *heart rate* is in the neighborhood of 80 per minute. The dose is then reduced to once or twice daily. Usually four or five days are required to slow the ventricular rate, but more or less time may be needed, depending on the individual. In an ambulatory patient, a  $1\frac{1}{2}$ -grain tablet may be safely given three times daily (after meals) for one week. In a very ill patient with a rapid ventricular rate and congestive heart failure the indication is for digitalis intravenously. In these emergencies quick action of the drug may be life-saving. A purified tincture should be used in doses of 4 cat units and repeated in four hours. The drug can also be started by mouth.

Intramuscular or subcutaneous injection of these preparations is *not* to be recommended. One would hardly expect a drug

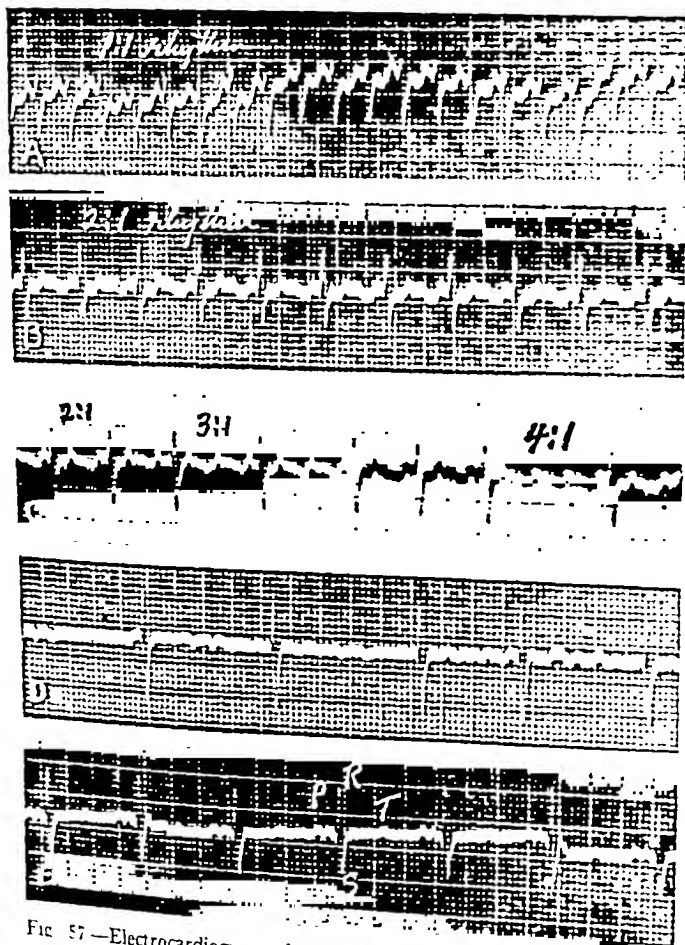


FIG 57—Electrocardiograms from a patient with auricular flutter, showing the effects of digitalis therapy (all Lead II) A, Record obtained during a short paroxysm of 1:1 flutter (no heart block). Auricular and ventricular rate 270 per minute. B, 2:1 heart block. Auricular rate 272. Ventricular rate 136 (before treatment). C, Record after 30 grains of digitalis leaves. Auricular flutter with 2:1, 3:1 and 4:1 heart block. D, After 36 grains digitalis leaves. Auricular fibrillation. Ventricular rate about 70. Note the change in the waves caused by auricular activity. Digitalis stopped. E, Return to normal sinus rhythm. Auricular and ventricular rates 82 per minute.

which is irritating and poorly absorbed to be efficacious when the circulation is failing.

In *auricular flutter* digitalis is also the drug of choice. Large doses are often needed and close observation of the patient is essential. The drug is given in divided doses totalling 6 to 9 grains daily and continued until slowing of the ventricle occurs. Reversion to auricular fibrillation is the rule and if the drug is then stopped many of the patients will return to normal rhythm (Fig. 57). In some patients auricular fibrillation continues after the flutter has been eliminated by the digitalis therapy. In these instances digitalis should be continued in sufficient dosage to control the ventricular rate, fibrillation being a much more satisfactory rhythm to control than flutter.

The maintenance dose of digitalis varies considerably and again shows little relation to the weight of the patient. It is best determined by clinical trial. The most frequent satisfactory dose is  $1\frac{1}{2}$  grains of the powdered leaves daily. The important thing in auricular fibrillation is to give sufficient of the drug to keep the heart at 70 to 80 per minute. This may take from  $\frac{3}{4}$  grain to 3 grains daily. Counting the heart rate by auscultation is always necessary, the pulse rate being unreliable if the heart rate is much above normal.

If difficulty is found in controlling the heart rate in auricular fibrillation several things should be considered. The most frequent cause is insufficient digitalis, and this factor should be carefully checked from all angles. An unrecognized hyperthyroidism may keep the heart rate above normal. Frank exophthalmic goiter will seldom be overlooked but a mild degree of thyrotoxicosis may be superimposed on existing heart disease and be the cause of marked disability. Proper treatment of the thyroid condition may restore the patient to fairly good health, whereas if the thyrotoxicosis remains unrecognized, cardiac compensation may be impossible.

Toxic effects of digitalis, affecting the rhythm, are more difficult to detect clinically when auricular fibrillation is present. Rarely, the ventricular rate may *increase* with treatment as the result of many ventricular premature beats. It is hardly possible to detect this condition clinically though it is easily determined by the electrocardiogram. More often, premature beats appearing as the result of treatment occur when the heart rate is relatively slow and can be suspected

clinically by the closeness of the beat and the coincident pulse deficit. It should be noted that auricular fibrillation may occasionally be a *manifestation* of digitalis toxicity. Occurring during the treatment of a patient with normal rhythm the heart rate is usually slower with the onset of auricular fibrillation and even complete heart block may coexist with this rhythm. On removal of the digitalis normal sinus rhythm will usually be resumed.

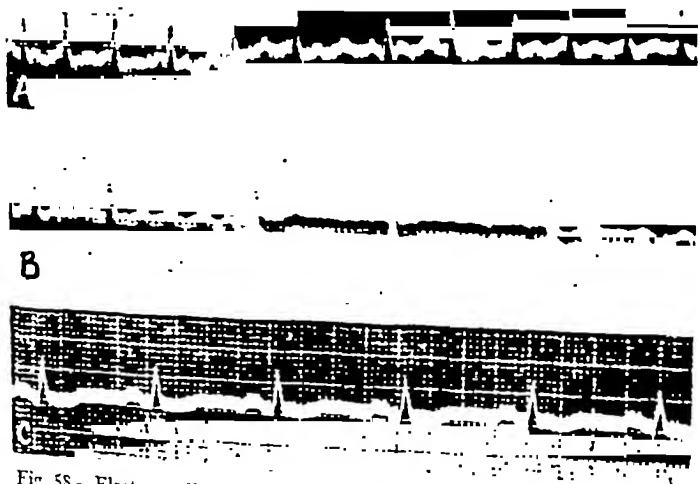


Fig. 58.—Electrocardiograms to illustrate the treatment of auricular fibrillation by quinidine therapy (all Lead II). *A*, Before any therapy was begun. Ventricular rate about 165 per minute. *B*, After 27 grains of digitalis leaves. Auricular fibrillation still present. Ventricular rate about 75 per minute. *C*, After 33 grains of quinidine sulfate (over a forty-eight-hour period). Return to normal sinus rhythm. Auricular and ventricular rates 76 per minute.

Quinidine sulfate is a valuable drug in the treatment of certain patients with auricular fibrillation. Its action is nearly the antithesis of that of digitalis. It decreases cardiac irritability and tone. When successful in the treatment of these cases the circus movement in the auricles is interrupted with a return to normal sinus rhythm. The immediate and ultimate success depends on the proper selection of cases, only a small number of the total being suitable. The ideal cases for this form of therapy are those in which auricular fibrillation is the only evidence of heart disease. Patients with only slight evi-

dences of heart disease and auricular fibrillation of short duration will usually have satisfactory results. Thyrotoxicosis cases in which normal rhythm does not obtain after elimination of the toxic factor are good cases for this therapy. *Contraindications* to this drug are long-standing auricular fibrillation (over six months), marked cardiac enlargement and the presence of signs of heart failure. In using quinidine sulfate to terminate auricular fibrillation it is wise to digitalize the patient first to control the ventricular rate (Fig. 58). The digitalis is then stopped and one dose of quinidine (3 grains) given to test for sensitivity. If no untoward reaction occurs it is begun in doses of 3 grains every four hours, when awake. The second day it may be given every three hours, and the third day 6 grains every four hours. This dosage may be continued for a total of one week. Larger doses are advocated by some and may occasionally be successful when smaller amounts of the drug fail. After return to normal rhythm the dosage of quinidine may be gradually "tapered off" over a period of a few days. Occasionally it may be wise to continue quinidine in doses of 10 to 15 grains daily over a long period of time. Rarely, digitalis and quinidine may be given simultaneously. An indication for both drugs might be as follows: a patient with organic heart disease in which digitalis was indicated, having also frequent attacks of paroxysmal tachycardia. Such attacks might be lessened in frequency and duration by the judicious use of quinidine in divided doses. Exceptions to the contraindications given may occur but in general it is wise to adhere rather closely to these. Fatalities occurring after quinidine therapy are exceedingly uncommon when the cases are properly chosen.

In summary, it is hoped sufficient emphasis has been placed on the clinical differentiation of the important disturbances in cardiac rate and rhythm. Space has not permitted a complete discussion of the subject, some of the less important arrhythmias as sino-auricular block and A. V. nodal rhythm being omitted. Heart block is considered only in differential diagnosis. Finally, it should be stated that the court of appeal in difficult cases is the electrocardiogram. Familiarity with and more frequent use of this method of examination will improve one's clinical diagnostic ability.

## CLINIC OF DR. EDWARD WEISS

TEMPLE UNIVERSITY

### SYMPTOMS OF HEART FAILURE IN HYPERTENSION

RECENT studies by the Metropolitan Life Insurance Company show that every other individual past the age of fifty in the United States dies of cardiovascular-renal disease. More than one half of this number are cardiac deaths and the greatest single cause is hypertensive-vascular disease. This indicates the importance of the topic assigned, that is, the symptoms of heart failure in hypertension. But essential hypertension is not the only variety of hypertension that produces heart symptoms. Heart complications also occur in glomerulonephritis, both the acute and chronic varieties, sometimes during the course of the toxemia of pregnancy and also in congenital stenosis of the isthmus of the aorta. These latter causes, however, are probably responsible for only about 5 per cent of the instances of heart disease due to hypertension. All the rest are due to the condition that is usually termed "essential hypertension." It is hardly necessary to spend much time discussing what is meant by that.

The generally accepted concept of essential hypertension is a vasospastic disorder, widespread in the civilized world, that manifests itself chiefly in middle life, usually runs a course of about ten to twenty years after its discovery, leads gradually to thickening and constriction of the smaller vessels so that life eventually is terminated by failure of one or another of the vital organs—heart, brain or kidneys.

### PATHOGENESIS OF HEART FAILURE IN HYPERTENSION

This brief statement must suffice to introduce us to the important relationship that exists between essential hypertension and heart disease. It leads the list of the causes of heart

failure. How then is this heart failure brought about? The explanation is not clear in all cases but in the majority after essential hypertension has persisted for a period of years hypertrophy of the left ventricle of the heart occurs. So well is this fact recognized that when we meet with hypertrophy of the heart that is not due to a valvular defect it can almost always be explained on the basis of essential hypertension. But the question arises why does the hypertrophied heart fail? And again the answer to this question is almost as obvious as the cause of the hypertrophy—failure occurs because of coronary artery sclerosis which interferes with the nutrition of the heart muscle. This introduces us to a more difficult question; that is, the relationship between coronary artery sclerosis and essential hypertension. Coronary artery sclerosis occurs as a part of a more widespread atherosclerosis which affects principally the aorta and its branches—a senile, degenerative process of the large vessels not necessarily related to essential hypertension. The day has fortunately passed when we considered that arteriosclerosis was responsible for essential hypertension. Now we know that essential hypertension is a vasospastic process which precedes arteriosclerosis rather than follows it. We also know that this latter form of arteriosclerosis is a diffuse hyperplastic sclerosis affecting small vessels, an *arteriolosclerosis*, in contrast to the above-mentioned senile, degenerative process which affects larger vessels. I prefer the term “hypertensive-vascular disease” for the one form and atherosclerosis, which may occur entirely independently and is certainly of another origin, for the other. Nevertheless, the two processes are frequently associated, that is, they coexist, mainly because essential hypertension is the most frequent disorder of middle life and atherosclerosis is the most frequent disorder of later life and individuals with essential hypertension live into the age period when they develop atherosclerosis. It is probably also true that when these processes coexist their development is accelerated. Hence it is that essential hypertension is frequently complicated by coronary artery sclerosis. Under such circumstances the individual is in greater danger than if either process existed alone because the heart is forced to work harder as a result of the essential hypertension and at the same time a slow but certain interference with the nutri-



tion of the heart is occurring. So we may say that the ability of the heart to carry on in the presence of essential hypertension depends largely upon the integrity of its blood supply through the coronary vessels. These statements we may accept for our clinical purposes although it is quite true that there are instances of failure of the heart in the course of essential hypertension that cannot be explained on the basis of coronary artery disease.

The question with which we are immediately concerned is—how does this failure of the heart in the course of hypertension manifest itself?

#### ONSET OF HEART FAILURE

Evidences of heart failure may be insidious or sudden in onset. For a long time, in the majority of instances, there are no symptoms. During this period hypertrophy of the left ventricle is taking place but since the heart is entirely capable of meeting all demands made upon it no symptoms occur. The first and most important symptom that occurs is shortness of breath on exertion and it may precede by months or years any further evidence of heart disease. However, other symptoms may occur concomitantly or follow in quick succession after shortness of breath occurs. Palpitation is a frequent symptom and may occur with or without a disturbance in the rhythm of the heart. One of the most frequent and important disturbances in rhythm in the hypertensive form of heart disease is auricular fibrillation. It is a serious complication, the anatomic basis of which is atherosclerosis, an associated mitral stenosis or thyroid disease. It may also occur in association with coronary thrombosis and occasionally as a functional disturbance. In the latter instance it is not so serious as when due to the previous causes mentioned. Other disturbances in rhythm are paroxysms of tachycardia and premature beats. When heart failure has advanced to a serious degree gallop rhythm may make its appearance and must be carefully sought for because of its prognostic value.

As heart failure continues, dyspnea becomes more pronounced, cough and expectoration follow, and finally orthopnea is established. As complete failure sets in, and frequently in association with gallop rhythm, early Cheyne-Stokes breathing

makes its appearance. This disturbance in respiratory rhythm can often be observed best at night or at times when the patient dozes off. Dyspnea of heart failure may be associated with or exaggerated by other causes of dyspnea such as obesity, pulmonary emphysema, kidney disease, anemia or psychic factors. Its relationship to the dyspnea of emphysema is an important consideration frequently neglected. It often happens that an individual with dyspnea which is thought to be of cardiac origin has a perfectly normal heart but suffers from pulmonary emphysema. Frequently such patients are told that they have heart disease and dosed with digitalis when in reality the dyspnea is bronchial in origin and the heart is normal or nearly so. In regard to the latter question it also frequently happens that both heart disease and pulmonary emphysema are present so that the dyspnea is of combined origin. If possible we must attempt to evaluate this dyspnea by saying how much is due to the cardiac disease and how much is due to the coexisting pulmonary emphysema. Dr. Morris Kleinbart and I have worked on this problem by circulatory measurements—velocity time and venous pressure estimations—in addition to special fluoroscopic studies made by Dr. Hugo Roesler. We believe that we have been helped by these special observations in determining in many instances of combined chronic heart and lung disease which was the more important factor in the production of dyspnea.

#### CARDIAC ASTHMA: LEFT HEART FAILURE

This differentiation of heart and lung causes for shortness of breath becomes even more important under another set of circumstances. This brings us to the consideration of a form of dyspnea that occurs in heart disease that is just as important as the dyspnea of exertion and that is dyspnea that occurs chiefly at night as a paroxysm and is usually referred to as an attack of cardiac asthma. Usually the clinical differentiation from bronchial asthma is not difficult but under some circumstances, especially in the elderly, it may be impossible to say whether this paroxysmal attack is cardiac asthma or true bronchial asthma. It is an important problem because the prognosis and treatment differ so markedly in the two groups.

A patient with essential hypertension, who has dyspnea on

exertion and perhaps other symptoms such as fatigue and palpitation, awakens suddenly one night with agonizing shortness of breath which causes him to sit up in an effort to get sufficient air into his lungs. He may even get out of bed or rush to the window for air. This paroxysm of dyspnea is frequently accompanied by cough and it may be by the expectoration of blood-tinged, frothy sputum. When this happens it is definite evidence that pulmonary edema has occurred and indicates clearly the nature of the attack—sudden failure of the left ventricle. If we are fortunate enough to observe the development of an attack we will note frequently an increase of blood pressure prior to the onset, an accentuation of the pulmonary second sound indicating the hypertension in the lesser circulation, and during the attack the presence of numerous moist râles over the bases of the lungs. Not a great deal is known about the actual mechanism of cardiac asthma but we do know that it comes especially at night and it may be that the position of the patient interfering with diaphragm action has something to do with the onset of the attack. Various other circumstances seem to bear a relationship to the attack, such for example as gastric distress, bowel or bladder discomfort, or even an anxiety dream. Cases have been described to me which seemed to follow directly after coitus.

#### FAILURE OF THE RIGHT SIDE OF THE HEART

Both varieties of dyspnea that we have discussed, dyspnea on exertion and paroxysmal dyspnea, are evidences of left heart failure, the one gradual and the other sudden. Meanwhile the right heart is responding by hypertrophy to the increased tension of the lesser circulation caused by the chronic left heart failure. Eventually the right heart fails, unless the individual meanwhile succumbs to an attack of pulmonary edema, coronary occlusion, or some accident unrelated to the heart disease, and then added to the evidences of pulmonary congestion are the signs of increased venous pressure and visceral congestion. That is, we now may observe a little edema of the dependent portions of the body, such for example as ankle edema occurring in the evening, an enlarged and tender liver responsible for indigestion, albuminuria due to renal congestion, and an increased venous pressure which can be observed

as a distention of neck veins or a failure of the arm or hand veins to empty as readily as in the normal individual when the arm is raised above the level of the auricle. At about the same time we may often observe, especially in fluoroscopy, a little fluid at the bases of the chest, obliterating the costophrenic angles. The pulmonary congestion of left heart failure with prominence of the pulmonary conus can also be readily observed fluoroscopically. And of course in time pleural collections may occur as well as abdominal ascites or even a general anasarca. It is important to remember that edema may be accumulating before it manifests itself by pitting and it is also well to remember that in hospital patients or patients who have been in bed for a period of time the edema collects in the dependent portions as for example in the thighs, around the buttocks and in the sacral region. Many other symptoms make their appearance during this period of failure but just how closely they are related to the insufficiency of the heart is a little difficult to state. I am thinking of neurologic and mental symptoms such for example as headache, dizziness, tinnitus and changes in disposition such as irascibility, childishness, fits of depression, persecutory delusions and actual periods of psychosis.

#### ANGINA PECTORIS: PAINFUL HEART FAILURE

And now we must consider an entirely different syndrome that occurs in the course of heart disease associated with essential hypertension. I refer to the condition known as angina pectoris. This syndrome of characteristic pain with typical distribution is sometimes referred to as painful heart failure in contrast to the congestive heart failure that we have just discussed. It is now quite generally accepted that in the majority of instances of angina pectoris, coronary artery disease is responsible. Just why coronary artery disease should be responsible for a painful affection of the heart in one individual and for congestive heart failure in another is not clear. But just as we stated that there are instances of congestive heart failure in the course of essential hypertension that do not show any evidence of coronary artery involvement so there are cases of angina pectoris in which the coronary arteries are free from disease or in which the sclerosis is so slight that it cannot be

held responsible. We presume that vasospasm of the coronary arteries must play a part here. Certainly it is generally accepted that anoxemia of the heart muscle is the mechanism behind the painful affection in the same way that we look upon intermittent claudication as a disorder dependent upon disturbed nutrition and anoxemia of the calf muscles. There are many kinds of precordial pain but there is no mistaking the characteristic attack of angina pectoris. Its association with effort or excitement, its position under the sternum, its characteristic squeezing, constricting or oppressive nature and its well-known distribution, together with associated general anxiety features and the abolition of pain by the use of nitrites make it unmistakable.

### CORONARY OCCLUSION

The profession has also become very familiar with a closely related and even more serious disorder of the coronary arteries and that is sudden occlusion, the result of which is infarction of a portion of the heart wall. The middle-aged, sthenic type of individual with hypertension who develops attacks of angina pectoris is a candidate for an attack of coronary occlusion. The characteristic seizure is now so well known that we need not take time to discuss it. Nor need we for the same reason spend time discussing the differential diagnosis from the upper abdominal emergencies. It is not so well known that another variety of vascular accident often associated with hypertension may be confused with coronary occlusion and that is rupture of the aorta and the formation of a dissecting aneurysm. In this condition the pain is frequently felt in the back, between the shoulder blades or lower as progressive splitting of the aortic coats takes place. Pulmonary embolism with evidence of acute right heart strain now referred to as acute cor pulmonale is sometimes mistaken for coronary occlusion. The similarity may be very close even to the presence of a pericardial friction rub. Spontaneous pneumothorax causing pain and shock has been mistaken for coronary occlusion but once seen is not likely to be again confused. It is well known that the patient with angina pectoris may later develop congestive heart failure following which there is relief from pain. The reverse situation has also been noted, that is, congestive heart

failure that clears up and is followed by angina pectoris. Sometimes pain and congestive failure occur together.

#### THE IMPORTANCE OF PERSONALITY STUDY IN HYPERTENSIVE HEART DISEASE

Although not strictly concerned with the title of this presentation I next want to consider a group of symptoms that may seem to be connected with heart disease occurring in the course of essential hypertension but in reality have nothing to do with the heart. The first is pain in the precordium which must be differentiated from angina pectoris, the second is fatigue that is out of proportion to the amount of physical impairment, and the third is usually described as shortness of breath although it actually is not dyspnea and must not be confused with it. In regard to pain in the precordium in patients with essential hypertension the variety that I speak of does not necessarily occur with exertion but may come on at any time and often does so while the patient is at rest. It is not placed as typically as angina pectoris nor does it have the distribution of true angina. It is frequently described as a soreness or as sticking, burning or lancinating and as one examines the patient the pressure of the palpating hand or of the bell of the stethoscope produces the pain which the patient complains of. Such a pain has nothing to do with coronary artery disease and it is very important to differentiate it. In reality it is a symptom of cardiac neurosis, often erroneously referred to as the effort syndrome. It frequently arises in the course of hypertension because such patients are told that they have heart disease—"an enlarged and leaking heart"—or they suspect, because of common knowledge regarding high blood pressure, that heart disease has developed. A symptom frequently associated is "sighing respiration" which is frequently referred to by the patient as shortness of breath. What the patient really means and will graphically describe is that there is a sense of pressure under the lower part of the sternum which she tries to relieve by taking a deep breath and she sometimes finds herself unable to do so. This is not dyspnea and it has nothing to do with heart failure so that again it is very important to differentiate this symptom. I have been particularly impressed by the presence of these symptoms in women who

have hypertension, especially that variety which appears at the menopause. If we remember, as has so well been pointed out by Levy and Boas, that coronary artery disease is uncommon in women and if we further remember that women seem to stand the effects of hypertension very well we will be on our guard against making a diagnosis of true angina pectoris in a female patient with hypertension. Not that it cannot occur but it is not so common as in men.

These are practical considerations because in studying a patient with essential hypertension it often becomes just as important in one case to reassure the patient in regard to his ability to carry on as it is in another case to urge rest. In order to estimate just how much activity may be permitted or on the other hand how much rest a patient should have we must carefully correlate symptoms, physical signs and laboratory results. This means that physical measurements—blood pressure determinations, heart size, eyeground studies, renal functional estimations—are essential in understanding the physical status of the hypertension patient but that personality studies are equally important in estimating his ability to carry on or his need for restrictions and rest.

#### TERMINOLOGY IN HYPERTENSIVE HEART DISEASE

Lastly, I would like to say something about the term "chronic myocarditis." Fortunately we do not meet it as frequently as we formerly did. In the majority of instances what is called "chronic myocarditis" is hypertensive heart disease either with or without coronary sclerosis. Now while it is true that certain myocardial changes occur under such circumstances which often can be demonstrated by electrocardiographic study this in reality is not a myocarditis although it may be termed "myocardial degeneration." I see no necessity for using the term at all. It is just as simple and much more precise to speak of hypertensive heart disease either with or without coronary artery sclerosis.

In conclusion I have tried to indicate that the ability of the heart to function properly in patients with essential hypertension apparently depends upon the integrity of the coronary vessels. Hypertension can exist without coronary artery sclerosis and of course the reverse is true that coronary artery

sclerosis exists without hypertension but when they coexist the situation is unquestionably more dangerous for the individual. Then it is that obesity, complicating disorders such as diabetes and gallbladder disease, renal impairment and intracranial vascular accident add to the complexity of the problem. Physical and mental stress may act to bring about sporadic increases of blood pressure and thus precipitate heart symptoms either in the form of gradual failure, sudden paroxysmal dyspnea, angina pectoris or coronary occlusion. Sometimes because of the vascular disease that goes on with regard to the other viscera an almost simultaneous disintegration of vital organs occurs. Then it becomes difficult to say whether heart, brain or kidney failure is the cause of death.

We may end this discussion by stating that in the course of hypertensive heart disease, failure of the heart is usually determined by coronary artery sclerosis which impairs the nutrition of the heart muscle. The first symptom is most often dyspnea which occurs on exertion or may occur suddenly—paroxysmal dyspnea (cardiac asthma)—followed by right heart failure producing increased venous pressure, evidences of visceral congestion and edema of the ankles. Quite apart from this congestive heart failure a painful heart affection known as angina pectoris may occur which sometimes is terminated by congestive failure or by coronary occlusion. But coronary occlusion may occur as an independent affection without any history of previous angina. Lastly, either in association with congestive failure or occurring without any clear evidence of heart disease are a number of symptoms which are psychic in origin. They must be sharply differentiated when they exist alone and carefully evaluated when they exist in combination with hypertensive heart disease.



## CLINIC OF DR. MARY HOSKINS EASBY

### PRESBYTERIAN AND WOMAN'S HOSPITALS

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#### THE EARLY RECOGNITION OF CARDIAC INSUFFICIENCY IN THE PRESENCE OF PREGNANCY

THE importance of the early detection of cardiac insufficiency during pregnancy is emphasized by the statistics of a recent maternal mortality report published by the Philadelphia County Medical Society.<sup>1</sup> In this three-year study there were 69 maternal deaths with heart disease as a factor; in 16 cases heart disease was the primary, in 53 the secondary cause of death. This figure represents 9 per cent of the total deaths of the series. Of the 78 maternal deaths with nonobstetrical conditions as their primary cause, heart disease is second only to pneumonia. From a study by Fraser<sup>2</sup> comes the statement that among all causes of maternal deaths not due primarily to pregnancy, heart disease stands second only to nontuberculous lung disease. Forty of the 69 patients in the Philadelphia County Medical Society report, whose deaths were caused by or complicated by heart disease, had shown complications during previous deliveries. It seems justifiable to conclude from such figures that a substantial improvement in the maternal mortality rate might be effected if this group of cardiac deaths could be eliminated or markedly reduced.

The observations which are presented in this study were made in the cardiac clinics of the Presbyterian and Woman's Hospitals of Philadelphia. The collection of data on pregnant patients was begun at the Woman's Hospital in 1931, and extended through the middle of 1936. At the Presbyterian Hospital observations were made during the years 1934, 1935, 1936. The total number of patients passing through the prenatal clinics of these two hospitals during the years under consideration was 3059; of this number, 258 were referred to

the cardiac clinics for study because of the presence of abnormal cardiovascular signs and symptoms. These patients were all examined before delivery and whenever possible were seen after delivery. When patients failed to return for check-up after their confinements, their hospital records were studied to determine the cardiac diagnoses at the time of their discharge. Those who were considered to have organic heart disease have, with few exceptions, been seen and reexamined at least once since their deliveries; many of them attend heart clinic regularly. Three cases without postpartum data were discarded from the series.

Of the 255 who are included, 42 were found to have organic heart disease; this is 1.37 per cent of the total number of patients passing through the prenatal clinics of the two hospitals. This figure is comparable with the data given by Herrick,<sup>3</sup> who found that 1 per cent of all pregnancies are complicated by cardiac disease, and that 6 per cent of these die. White<sup>4</sup> found that 2 per cent of pregnant women have symptoms and signs of heart disease, and that 1 per cent has organic heart disease. Lamb<sup>5</sup> found organic heart disease in 2.7 per cent of pregnant women in a four-year study. Sodeman<sup>6</sup> states that, in general, the incidence of heart disease in pregnancy is about 1 per cent.

Of the 42 cases, 12 or 28.6 per cent showed some degree of congestive failure during pregnancy or at the time of delivery; the number of deaths was three. A brief review of these cases follows. In making the diagnoses, the functional classification approved by the American Heart Association was used.<sup>7</sup>

**Case I.**—Age twenty-six years. This patient was first seen between the first and second months of her first pregnancy. Her diagnosis was congenital heart disease, pulmonary stenosis, cardiac enlargement, right ventricular preponderance, normal sinus rhythm, Class II B. She was hospitalized during almost her entire pregnancy, and although seen early and presenting evidence of congestive failure during the entire time she was under observation, pregnancy was not interrupted because there was a persistent gonorrheal infection which did not clear up until almost the end of the prenatal period. At times her functional classification was Class III, but adequate therapy

restored her to Class II B; she was allowed to go to term and was delivered with forceps of a normal male child. Some evidence of failure was present during the puerperal period, but this gradually cleared up. This patient attends cardiac clinic regularly. Her present functional classification is II A.

**Case II.**—Age thirty-nine years. This patient showed failure when seen in the seventh month of her ninth pregnancy. She gave no history of failure previously during her long period of childbearing. Her etiology was undetermined; the anatomic diagnosis was cardiac enlargement with mitral insufficiency, left ventricle preponderance; she had a normal sinus rhythm throughout, her functional classification was Class II B. She was hospitalized and given appropriate medication for congestive failure; there was sufficient improvement for the patient to go home until she was at term. She returned to the hospital and was delivered spontaneously. At the time of delivery and during the puerperium she had some decompensation; she has been classed as II B since the time of delivery.

**Case III.**—Age twenty-one years. When first seen she was in her seventh month of her first pregnancy. Her diagnosis was rheumatic heart disease with cardiac enlargement, mitral insufficiency, mitral stenosis, right ventricle preponderance, and auricular fibrillation; she was classed as II B. She was hospitalized a few days after her first examination and remained in the ward until three weeks after delivery, a total of ten weeks. She was given appropriate therapy and at term had reestablished compensation. A cesarean section was done and the patient left the hospital in fair condition. She attends cardiac clinic regularly and still has sufficient cardiac disability to be classed as II B.

**Case IV.**—Age twenty-three years. This patient was three months pregnant when first seen in clinic. The pregnancy under consideration was her second, and she gave no history of failure with the first. She was diagnosed as follows: rheumatic heart disease, cardiac enlargement, mitral insufficiency, mitral stenosis, right ventricle preponderance, normal sinus rhythm; functional classification Class II A. She showed in-

creasing cardiac disability, and the classification was changed to II B within a month after her initial examination. She was hospitalized several days before delivery, and showed improvement with digitalization; a cesarean section was done and the patient was sterilized. Three days after operation she had an acute right-sided heart failure with auricular fibrillation; she recovered from this, and after seven weeks' hospitalization, went home in fair condition. She attends cardiac clinic and is classified as II B.

**Case V.**—Age twenty-five years. She was first seen in the third month of her second pregnancy; no failure had occurred with the first. She was found to have rheumatic heart disease with mitral insufficiency and stenosis and gallop rhythm, and was placed in Class II B. Because of cardiac insufficiency, she was hospitalized ten days before delivery and given appropriate therapy. After compensation was restored, a cesarean section and sterilization were done. She showed some signs of failure during the puerperium, but improved and was sent home in good condition. She attends cardiac clinic, and has remained in Class II A since her discharge from the hospital.

**Case VI.**—Age twenty-one years. This patient, who was first seen in the second month of her second pregnancy, gave no history of previous failure. She was found to have rheumatic heart disease with cardiac enlargement, mitral insufficiency, mitral stenosis, normal sinus rhythm, and she was classified as II B. In addition to signs of congestive heart failure, she had persistent vomiting, weight loss, temperature rise and nosebleeds. Pregnancy was terminated because of rheumatic activity after the patient had been hospitalized long enough for compensation to be restored; she was subsequently sterilized. Her recovery was uneventful. She attends cardiac clinic regularly, and has remained in Class II A since leaving the hospital.

**Case VII.**—Age twenty-one years. This was the patient's first pregnancy and she was in her sixth month when first seen. She was found to have rheumatic heart disease with cardiac

enlargement, mitral insufficiency, mitral stenosis, with normal sinus rhythm. She was in marked failure, Class III, and was hospitalized. She improved on appropriate medication and was permitted to go home on a strict regimen of rest and digitalis. Later in her pregnancy it was necessary to hospitalize her again for seven days; she again improved, went to term, and was delivered by a cesarean section. Sterilization was done, and subsequently the patient left the hospital with compensation reestablished. No follow-up examination has been possible.

**Case VIII.**—Age twenty-seven years. This patient was first seen in the seventh month of her second pregnancy. Her diagnosis was rheumatic heart disease, cardiac enlargement, mitral insufficiency, a slight degree of coronary sclerosis, normal sinus rhythm, Class II B. She gave a history of having had sufficient cardiac disability with the first pregnancy, to have needed bed rest for a period of several weeks and delivery by cesarean section. In the pregnancy under consideration, she was carried along to term and was delivered by forceps of a stillborn child. Later she came in near the end of her third pregnancy and was hospitalized and delivered by cesarean section because of evidence of congestive failure and small measurements. Her recovery was uneventful and she left the hospital with compensation restored. Unfortunately this patient has been lost sight of, and no follow-up examination was possible after discharge from the hospital.

**Case IX.**—Age thirty-two years. This patient was first seen between the seventh and eight months of pregnancy. She had rheumatic heart disease with cardiac enlargement and mitral stenosis, and showed definite evidence of myocardial fibrosis by electrocardiogram; she had normal sinus rhythm and was classed as II B. She had had 4 previous pregnancies, but gave no history of previous failure with any of them. She improved with rest and digitalization, and about 1 month after her first cardiac examination, labor was induced. Her recovery was uneventful. About ten days later she was sterilized; she recovered and left the hospital in good condition and has shown no evidence of failure since.

**Case X.**—Age twenty-eight years. This patient was first seen between the fourth and fifth months of her fifth pregnancy. She had rheumatic heart disease with cardiac enlargement, mitral insufficiency, mitral stenosis, sino-auricular tachycardia; she was in advanced failure (Class III), with a marked degree of pulmonary edema. She was immediately hospitalized and digitalization begun. Later on the same day of her admission to the hospital she had a premature separation of the placenta followed by death.

**Case XI.**—Age nineteen years. This was the patient's first pregnancy. She was first examined at six months and found to have rheumatic heart disease with cardiac enlargement, mitral insufficiency, mitral stenosis, early aortic insufficiency, and a possible adherent pericardium. The electrocardiogram showed normal sinus rhythm interrupted by auricular premature contractions and right axis deviation; she was classed as II B. She was put on a strict regimen of rest and digitalis with frequent reexaminations in clinic; no definite failure occurred during this period. At eight and one-half months she was admitted to the hospital for observation, and after about two weeks of complete rest, a cesarean section was performed. The patient had a cardiac arrest on the operating table but recovered. Following this she developed auricular fibrillation, and for three days her progress seemed fairly satisfactory under digitalis therapy. She then developed a *Staphylococcus aureus* blood stream infection and died ten days after operation.

**Case XII.**—Age twenty-five years. When this patient first came under observation she was five and one-half months pregnant; she had had no previous pregnancies. She was found to have rheumatic heart disease, cardiac enlargement, mitral insufficiency, mitral stenosis, right ventricular preponderance, normal sinus rhythm, and she was put into Class II B. She was followed for a month and a half in clinic during which time she presented no definite evidence of failure. At seven months she went abruptly into failure with an attack of nocturnal dyspnea; unfortunately she did not report to the hospital until four days later at which time she was in advanced

failure (Class III). She was then admitted to the ward and an effort was made to digitalize her. Her condition was too serious to permit of interruption of pregnancy. Digitalis and bed rest failed to restore compensation in any degree and four days after admission she delivered spontaneously and the following day died in failure.

In this group of 12 cases presenting cardiac failure, one was first seen between the first and second months of pregnancy, 2 were seen at three months, 1 at four months, 1 at four and one-half months, 1 at five and one-half months, 2 at six months and 4 at seven months; 5 were primiparae, 4 were Gravida II, 2 were Gravida V, and 1 was Gravida IX. Only 1 of the multiparae had any history of failure with previous pregnancy; 11 were considered to have sufficient cardiac disability to be classed as II B at the time of their initial examination. The one who was in Class II A at the beginning of the observation period (three months) had gone into Class II B a month later. All but 2 had definite rheumatic histories, of these 2, one had a congenital lesion and the other gave no history of disease predisposing to organic cardiac change.

There were 3 deaths in the groups. Two of these, the one associated with the *Staphylococcus aureus* septicemia, and the one with the premature separation of the placenta, cannot be attributed to congestive heart failure alone, inasmuch as the associated conditions themselves carry a high mortality rate; the third case was one of uncomplicated congestive heart failure. We find, therefore, in this group that the percentage of patients dying of congestive failure alone is 8.33 of all who were in failure, and 2.38 of the entire organic group of 42 cases. This figure seems low, inasmuch as Herrick<sup>3</sup> states that 6 per cent of pregnant women with heart disease die; and Eastman<sup>8</sup> gives a mortality rate of 5 to 8 per cent after a widespread study in hospitals with and without special cardiac clinics. The explanation for this apparent low figure in my series is that cardiac death may occur during pregnancy or delivery without failure being present, and would therefore not be included in this study. Such cases would be death from emboli, from subacute bacterial endocarditis, etc. Also in the group of 42 organic cases studied, all except 6 were under close observation of both prenatal and cardiac clinics during that

part of pregnancy in which failure is most apt to occur, namely, the last two months. Whenever indicated, these patients were hospitalized for rest and observation, or put to bed at home under a regimen of rest and medication. One death occurred in the organic group which was not mentioned above because no failure was present; this case was one of rheumatic heart disease with mitral stenosis whose death occurred four days postpartum from a *Staphylococcus aureus* blood stream infection, but whose functional classification remained II A throughout the period of observation. This case added to the 3 already discussed gives us a total of 4 deaths associated with cardiac disease, but in 3 of which death could not be attributed to heart disease alone.

It would be justifiable to conclude that close observation in cardiac clinic as well as in prenatal clinic of the cardiogravid patient during pregnancy is a factor in reducing mortality from congestive failure. It enables the early signs and symptoms of failure to be detected and evaluated, and adequate treatment instituted. The detection of early failure in these patients is not without difficulty; Gammeltoft<sup>9</sup> states that 16.3 per cent of 239 normal pregnant women studied had signs and symptoms of heart disease; all of which cleared up soon after delivery, and did not improve on rest and digitalis. Hamilton and Kellogg<sup>10</sup> state that 7.5 per cent of all pregnant patients in a group they studied required a decision on the heart. The signs and symptoms presented by the noncardiac pregnant patient depend on the fact that new demands are made in pregnancy on circulation, and consequently on the heart. Stander and Cadden,<sup>11</sup> using the acetylene method of computing cardiac output, found an increase in cardiac output of more than 50 per cent in the latter half of pregnancy. Grollman<sup>12</sup> points out that there is a large increase in the area of the circulatory bed in pregnancy. In order to maintain a constant blood pressure without depriving other parts of the body of a normal blood flow, there must be an increased cardiac output. This suggests that the heart must hypertrophy during pregnancy, and brings up the disputed point of whether the enlargement seen in the latter months is actual or whether the organ seems enlarged because of a pushing upward by the gravid uterus with outward displacement of the apex impulse and frequently



with a marked degree of left axis deviation in the electrocardiogram. In any event, it is to be expected that a heart which has sustained damage from infection, and which has consequently a diminished reserve, will manifest evidence of disability more readily under the strain of pregnancy than an undamaged heart. Consequently the earlier in pregnancy failure appears the more serious is the outlook. It is therefore essential that patients with definite organic damage be seen as early as possible for cardiac study, that they report for reexamination at regular intervals during pregnancy, that they be seen during their hospitalization by a cardiologist when possible, and that they be referred back to cardiac clinic for postnatal check-up. This requires the closest cooperation between the obstetric and cardiac departments of the hospital.

As has been pointed out, symptoms of early cardiac insufficiency may appear in pregnant patients who have no organic cardiac disease. Of the group of patients studied by me, the 213 who were not included in the organic group, showed the following signs and symptoms: 139 had systolic murmurs at the apex or pulmonic areas, 114 had dyspnea, 7 had orthopnea, 67 had palpitation, 12 had definite edema.

The early detection of congestive failure in pregnancy depends, therefore, on the finding of those same classical manifestations of cardiac insufficiency as would be seen in a non-gravid cardiac patient, namely: dyspnea, orthopnea, easy fatigability, palpitation, edema, the appearance of a systolic murmur, cardiac enlargement, premature beats, engorgement of the neck vessels, etc. But in addition, each symptom and sign must be evaluated in the light of the gravid state, and the degree to which it is intensified as pregnancy advances be taken as a criterion of its prognostic value. The appearance of pulmonary edema, gallop rhythm, auricular fibrillation, paroxysmal nocturnal dyspnea, severe precordial or substernal pain or rheumatic activity, is always an indication of serious trouble. History in these cases is of the utmost importance. Since the etiologic factor in the great majority of these cases is rheumatic, a painstaking search for the history of past infections must be made. If found, such a positive history increases the likelihood that the abnormal cardiac findings are on an organic basis, and both treatment and prognosis must be

modified accordingly. When the patient gives a history of one or more breaks in compensation, the expectation of failure during pregnancy is greatly increased.

In considering treatment of heart failure in pregnancy, it must be kept in mind that pregnancy is a strain on the circulation, and when heart disease is present, pregnancy may precipitate failure where failure would not occur were pregnancy not in the picture. The first consideration under treatment, therefore, is prevention. Patients who are in failure or have had previous failures, either with or without pregnancy, must be prevented from undertaking motherhood. This same is true of patients with rheumatic activity, subacute bacterial endocarditis, or fixed hypertension. One cannot state that failure may be anticipated in the presence of certain valvular lesions and not in the presence of others. In my group of 29 organic cases in whom no failure occurred, 11 had well established mitral stenosis, and 1 had an aortic insufficiency associated with mitral stenosis. I believe that where mitral stenosis has been of such long standing that the cardiac reserve is definitely impaired, it should contraindicate pregnancy. If it is accompanied by auricular fibrillation, pregnancy should certainly be forbidden even where there is no definite failure, as there is always danger of fatal emboli. Aortic insufficiency is considered by some as a contraindication. In my series, 2 patients had this lesion, both associated with mitral stenosis; 1 did not go into failure, the other died in failure, but had also a positive blood stream infection.

I believe that prevention should extend to this length: that any pregnant patient with definite organic heart disease should be regarded as a potential case of failure because of the added burden which the gravid state places on an already impaired circulation, and because there is no known formula which will tell us which cases will go to term safely and which will not. In addition, there are many women with organic cardiac disease who may go through pregnancy safely, but who sustain greater impairment to their already damaged hearts as a result of it. Lamb<sup>5</sup> reports from a study of 50 cases of organic heart disease, over a four-year period, that 43 per cent of them were made worse by the ordeal of pregnancy. Where there is organic cardiac disease of such a nature as is known

to impair cardiac reserve, the patient should be warned before undertaking motherhood that her pregnancy and delivery will be fraught with risk. If she has passed through previous pregnancies safely, she should be advised strongly against undertaking another one, and if she has passed through previous ones with cardiac difficulty, further pregnancies must be forbidden.

The treatment of early failure in pregnancy is the same as in the nongravid state. Rest is of course the first therapeutic measure to be enforced. Rest in the hospital is preferable to rest at home in the majority of cases. Hamilton and Kellogg<sup>10</sup> state that "if a patient with heart disease develops decompensation during pregnancy, she belongs in a hospital until pregnancy is terminated." Digitalis therapy should be employed, the dosage being adequate to control the heart rate at 80 or below. If the patient improves on rest and digitalis, she may gradually be worked up to mild activity. If allowed to go home, she must be on a regimen of rest and a maintenance dose of digitalis; such patients should return for hospitalization ten to fourteen days before term. If there is no favorable response to these measures and failure progresses, further treatment will depend on the stage of pregnancy. Each case must be studied as an individual problem in determining whether or not, and when, pregnancy should be terminated. Pardee,<sup>13</sup> writing on conditions indicating therapeutic abortion, states that patients seen before the fourth month in Class II B or III, should be considered for therapeutic abortion. He says: "It should never be performed, however, until after a proper course of treatment by rest and digitalis. Such patients are always improved by this to some extent at least, and after improvement has progressed as far as it will, and there has been no further improvement for two weeks, it is time to decide on further management." Should abortion be decided upon, the method of choice must next be considered. During the first three months vaginal procedures apparently do not greatly disturb circulation, but from five to seven months the heart is probably less disturbed by abdominal operation. The choice of anesthesia presents another problem. Local anesthesia is of course the safest procedure if the patient is cooperative; on the other hand, cardiac patients stand ether well.

If the patient's failure can be controlled and she is carried on to term, cesarean section seems to be the method of delivery most advantageous because it permits of sterilization, avoids physical strain and also because it can be performed at a time which is optimum from the cardiac standpoint. On the other hand, the recovery stage from a nonoperative delivery is shorter. Hamilton and Kellogg<sup>10</sup> do not believe it is justifiable to do a cesarean section for the sake of sterilization on account of the greater risks of this method. They state that the majority of multiparous cardiacs are safest delivered by forceps at full term with sterilization some months later if desirable. Should the patient be delivered by the usual method, and should some cardiac insufficiency be present, it is important that her head be kept elevated throughout delivery, and that the second stage of labor be shortened and eased in every way possible.

The success of the treatment of congestive failure depends not only on early detection, but upon such other factors as the economic status of the patient, her intelligence and ability to cooperate, her religious affiliations, the avoidance of intercurrent infections, the willingness of the hospital to keep a patient with poor home conditions in the ward for weeks or even months of rest if necessary, and the absolute cooperation between the obstetrical and cardiac departments. Each case requires individual study and care. All the above-mentioned factors must be considered of the greatest importance if our efforts to reduce the mortality from cardiac disease in general and most particularly from congestive heart failure are to meet with success.

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### USE OF DRUGS IN CARDIOVASCULAR DISEASE

THE significant clinical developments in the course of cardiovascular disease which are influenced by the use of drugs may be listed as of three types; namely, congestive myocardial failure, cardiac pain, and abnormal heart action. Although some of these clinical features may be present more commonly in certain forms of heart disease, one or more of these conditions may occur in most any type of cardiovascular disease, and the treatment of them is essentially the same, irrespective of the etiology of the heart disease. The use of drugs, then, in patients presenting these features, may be considered as treatment indicated by symptoms and signs.

For the purpose of the subject under discussion cardiovascular disease is divided etiologically into five groups; namely, rheumatic heart disease, hypertensive heart disease and coronary arteriosclerosis, thyrogenic heart disease, syphilitic heart disease, and subacute bacterial endocarditis. Then, accordingly, the drugs used in the different types of heart disease should be referred to as treatment indicated by etiology.

#### I. TREATMENT INDICATED BY SYMPTOMS AND SIGNS

##### 1. CONGESTIVE MYOCARDIAL FAILURE

**Digitalis.**—Digitalis, the most useful drug in the treatment of congestive myocardial failure is especially efficacious in those cases in which auricular fibrillation with a high ventricular rate is also present. However, it has been demonstrated adequately that very satisfactory results can be obtained in cases of cardiac decompensation with regular

rhythm. Hypertension in itself is no contraindication to digitalis therapy.

The plan of digitalis administration should vary somewhat with the individual patient. First, one should determine whether the patient has had any digitalis within the past three weeks, and how much if possible, and if the patient has had digitalis during this time further digitalis should be given in smaller doses and more cautiously. If no digitalis has been given within three weeks, or the patient has never had any digitalis the decision rests between rapid digitalization in a few hours by massive doses and slower digitalization by smaller doses at less frequent intervals during the next three or four days or longer. A severe degree of decompensation in a patient who has had no digitalis is the prime indication for rapid digitalization, while slow digitalization may have some advantages in the milder form of decompensation or in the patient who has had a considerable or an unknown amount of digitalis.

At a time when the massive dosage method was first coming into wide use, inadequate results from digitalis were attributed to insufficient digitalis and properly so. No doubt the potency of many digitalis preparations was less certain then than now. The common method of calculation of the digitalization dose was on the basis of body weight, using such formulae as 30 mg. of digitalis folia, or its equivalent, per kilogram of body weight, or 1 grain per 5 pounds of body weight. Accordingly, for a patient weighing 154 pounds the calculated dose would be 2 Gm. or 31 grains of digitalis folia, or its equivalent. The dosage might be expressed in terms of cat units, the "cat method" being commonly accepted for pharmacologic assay, and 1 cat unit representing  $1\frac{1}{2}$  grains, the above total dosage being equivalent to approximately 20 cat units. Ordinarily, one quarter of the digitalization dose (in the above instance  $7\frac{1}{2}$  grains or 0.5 Gm.) was given for 3 doses, about four to six hours apart, making three quarters of the calculated dose received by the patient within an eight- to twelve-hour period. By this time some effect would be noted probably as diuresis from digitalis usually does not occur in any marked degree until two thirds to three fourths of the digitalization dose is given, and by this time some effect upon the pulse rate or digestive tract might be looked for. If the optimum effect were



not noted  $1\frac{1}{2}$  grains (0.1 Gm.) to 3 grains (0.2 Gm.) one to three times a day would be given until beneficial effect was obvious or early toxic effects resulted. A good therapist would get the desired effects but stop short of toxicity, fulfilling the directions of Withering: "Let the medicine be continued until it either acts upon the kidneys, the stomach, the pulse or the bowels; let it be stopped upon the first appearance of any one of these effects."

This method of administration is satisfactory for hospital practice or very carefully controlled house practice, but in cases where such close observation is not possible it has become common practice to count on the average optimum amount of digitalis for the averaged-sized adult (150 pounds) as about 20 grains of digitalis folia, or its equivalent in other preparations, given in divided doses as above stated, and to proceed to satisfactory digitalization from that point cautiously up to the maintenance dose.

Two factors enter into this problem; first, it is almost impossible to gage the dosage accurately by the body weight as a considerable portion of the body weight may be edema fluid, and second, the maintenance dose may be greatly different in individual cases. Usually, however, the patient will know something about his weight before the edema appeared or some estimate of the weight representing edema may be attempted, and calculation can be made accordingly. In general,  $1\frac{1}{2}$  grains of digitalis folia (or its equivalent) has been found to be the average maintenance dose, but it should be known that some cases are well maintained on less ( $\frac{3}{4}$  grain) or more (2 grains) than this, and only close clinical observation will control this factor.

Four methods of administration are available; namely, the oral, the subcutaneous, the intravenous, and the rectal. Only in very rare instances need any other than the oral route be employed. Digitalis folia and tincture of digitalis are entirely satisfactory for oral administration and, except in very unusual instances are there any obvious advantages of other preparations. An injectable form for intravenous and subcutaneous administration is necessary in cases demanding quick action and many proprietary preparations are now available in properly standardized forms, and the future promises more

stable solutions of this type. General principles of assay and dosage expressed above are sufficient in guiding treatment if dependable and in-date preparations are used. It is well to remember that tincture of digitalis, or other solutions of digitalis are almost as efficacious if given by rectum as by mouth, usually some dilution with normal saline being desirable.

If slower digitalization is employed a satisfactory method is to use  $1\frac{1}{2}$  grains or 3 grains, depending on rapidity desired, of digitalis folia three times a day until the therapeutic effect is obtained and then giving a daily maintenance dose. In using digitalis in the presence of thyrotoxicosis or pneumonia or any other toxic state it is advisable to give only about half of the calculated dose for digitalization and then proceed cautiously, as it may be difficult to differentiate any increased toxicity as due to the digitalis or change in the preexistent toxic condition.

Clinically it seems to make no difference in the average case whether digitalis folia or the tincture is used providing potent and well standardized fresh preparations are employed and given in sufficient doses. There is a fallacy in the suggestion that the dosage can be more accurately gaged with tincture as the individual dose may be varied by as little as 1 drop. Usually it is not possible to determine the optimum amount by such small margin and there is no practical advantage in attempting to do so. It should be remembered that a drop of tincture of digitalis from the average dropper is less than a minim (usually about 2 drops to the minim) and the only dependable way is to measure the dose in minims.

Other drugs in the digitalis series still in use are strophanthus, ouabain, squills, and apocynum. These drugs seem to present no clinical advantage over digitalis, and since digitalis preparations now are so dependable it seems much wiser in average practice to know how to give digitalis and use it. Perhaps on rare occasions strophanthin or ouabain should be used when the digitalis effect must be obtained very promptly as a life-saving measure, but these drugs need no consideration in the ordinary management of congestive failure. Except in very rare instances there seems to be no good reason to prefer some of the glucosides of digitalis, although advantages are claimed by some. Verodigen, a gitalin- or digitalein-

like fraction of digitalis is an example, said to be more readily absorbed than digitalis, and claimed to be better tolerated by the gastro-intestinal tract, but its potency,  $\frac{1}{240}$  grain of verodigen being equivalent to  $1\frac{1}{2}$  grains of digitalis folia, indicates the advisability of its use in specially selected cases and under facilities for very careful observation.

**Diuretics.**—Diuretics are valuable adjuncts to digitalis therapy and three general groups are available: the xanthine derivatives, certain mercury compounds, and several salts. One of these diuretics may be helpful when another has failed, or a combination may act favorably when no appreciable effect has been obtained by one or the other alone. The presence of gastro-intestinal symptoms, the necessity for prompt diuresis, the definite accompaniment of nephritis, and the physician's personal preference are factors that influence the choice of one or other of these diuretics in the beginning. Failure of this choice leads to trial of others or combinations.

Theophylline (theocin), theobromine sodium salicylate (diuretin), and theobromine calcium salicylate (theocalcin) are the commonly used representatives of the xanthine derivatives. These three often produce excellent diuresis, and all are better given in fairly large doses for a short period of time and repeated, than in small doses over a long period of time. These drugs, especially theophylline, may produce gastric irritation or mental aberration, but not commonly, and such occasion need cause no alarm as discontinuance of the drug is accompanied by fairly prompt clearing of these symptoms. Theophylline in doses of 5 to  $7\frac{1}{2}$  grains (0.3 to 0.5 Gm.), or theobromine sodium salicylate,  $7\frac{1}{2}$  to 10 grains (0.5 to 0.6 Gm.), or theobromine calcium salicylate, 15 grains (0.1 Gm.) three times a day for two days or 6 doses, usually proves a satisfactory way to give these drugs. If diuresis is to occur from the drug it will do so likely by this time. Although these three drugs all belong to the same group, occasionally one will produce a diuresis in the same patient who has had no appreciable effect from one of the other two.

The mercurial diuretics are very important in the treatment of congestive failure and properly have enjoyed widespread clinical use. Merbaphen (novasurol, a mercury urea compound), mersalyl (salyrgan, a mercury salicylate com-

pound), and mercupurin (a mercury theophylline compound), are the three representatives of this group. These drugs are prepared for clinical usage as a solution in glass ampules, to give 1 cc. to 2 cc., preferably intravenously, or intramuscularly, but never subcutaneously. Subcutaneous injection or leakage about the point of injection into the vein causes necrosis of tissue, so extreme care about injection is necessary. The use of a small caliber needle and dilution of the drug before intravenous injection are helpful in avoiding such accidents. A great deal has been written about the relative toxicity especially of the first two of these mercurials mentioned; the approximate percentage of mercury in the three compounds is: novasurol, 33.9 per cent, salyrgan, 39.6 per cent, and mercupurin, 41 per cent. One gathers the impression from the literature that salyrgan is less toxic than novasurol, and that mercupurin is no more toxic than salyrgan, and possibly less so. The two main factors thought to influence this apparent paradox are individual sensitivity to mercury, or greater tolerance by some patients, and the possibility that the toxicity depends on the chemical linkage of the mercury to the rest of the molecule rather than to the actual percentage of mercury present. While there is no clear preference of one of these drugs over the other, on the whole, clinical reports have seemed more favorable to the use of salyrgan or mercupurin. Clinical doses of these mercurials may be accompanied by some increase in the casts in the urine, and because of the effect of mercury on the kidney, their use in patients with nephritis is cautioned. However, in ordinary cases of congestive failure their use need not be curtailed, as the kidney irritation as determined by the urinary cast count quickly subsides, and the gravity of the situation justifies their use.

Salyrgan and the mercurial salt of mercupurin (mercurin) are now available in suppository form and these preparations produce diuresis comparatively favorable with the intravenous administration.

If these diuretics are effective the diuresis will occur within a few hours, so it is advisable to give the drug early in the morning, so as to least disturb the patient at night. The dose of any of these ordinarily used is 1 cc. to 2 cc.; it may be repeated in one week, or if occasion demands as often as twice

a week. In some instances the mercurials have been efficacious, when they have not been before, after three or four days taking 60 to 90 grains (4 to 6 Gm.) of ammonium chloride daily.

**Certain Salts.**—The acid-producing salts, calcium chloride, ammonium chloride, and ammonium nitrate, may serve as excellent diuretics when given in large doses, ranging from 90 to 180 grains (6 to 12 Gm.) daily. Ammonium chloride or ammonium nitrate is more commonly used, and is best given in enteric-coated pills in an effort to avoid gastric irritation. These drugs may be given in capsules with the meals. If they are to be given in liquid form a vehicle containing yerba santa makes the preparation more tolerable. At times a better diuretic effect is noted by giving these salts in the above doses for a few days then discontinue them for a few days. A neutral diet aids in decreasing the amount of the salt necessary, but this is difficult to follow out for longer than a few days unless dietetic service is available.

Potassium nitrate or potassium chloride in large doses, 120 to 180 grains (8 to 12 Gm.) daily have been found to produce satisfactory diuresis in many cases, caution being given in cases with severe renal insufficiency.

**Morphine and Sedatives.**—These drugs are very useful in the cardiac patient, to give them mental and physical rest, and morphine sulfate is especially effective in the acute distress of congestive failure, when used in moderate doses.

**Cathartics.**—In some instances cathartics, especially the salines, are very useful, but generally the extra effort of increased bowel movements is undesirable if other measures are effective.

In the foregoing discussion no distinction has been made between so-called "right ventricular failure" and "left ventricular failure," although the general picture of congestive failure represents essentially the result finally or predominantly of "right ventricular failure." Attention should be called to the acute paroxysmal dyspnea with or without "cardiac asthma" due to acute failure of the left ventricle. Morphine sulfate is indicated in such an attack; aminophyllin, intravenously, may be helpful; and in those cases tending to have associated "cardiac asthma" with pulmonary edema the mercurials may be of some value.

Aminophyllin, 0.24 Gm. (4 grains) given slowly intravenously, is very effective in relieving the acute distress of Cheyne-Stokes respiration, and an oral dose in the evening may prevent occurrence at night, or steady dosage of  $1\frac{1}{2}$  grains three or four times a day may offer freedom from this symptom.

## 2. CARDIAC PAIN

The most significant cardiac pain is that of angina pectoris and coronary thrombosis. Although of similar character in onset, location and distribution the treatment of the two is different in the use of the vasodilators. The vasodilators are contraindicated in coronary thrombosis, as shock is a part of the picture. The blood pressure as a guide will help to avoid giving the nitrites when the diagnosis may not at first be apparent.

The nitrites, theobromine sodium salicylate, and aminophyllin are the drugs of choice for angina pectoris. Of the nitrites, nitroglycerin and amyl nitrite are the quickest and shortest in action and therefore useful in the acute attack. Sodium nitrite and erythrol tetranitrate are more useful in an attempt to decrease the frequency and severity of the attacks. The same may be said of aminophyllin and theobromine sodium salicylate; aminophyllin is given in doses of  $1\frac{1}{2}$  to 3 grains (0.1 to 0.2 Gm.) three times a day or sometimes  $1\frac{1}{2}$  grains five or six times a day is more effective. Theobromine sodium salicylate is given much the same way, the dose being  $7\frac{1}{2}$  grains (0.5 Gm.).

For coronary thrombosis morphine sulfate and aminophyllin are more effective. Morphine sulfate may and should be given in large doses, in the severe case  $\frac{1}{2}$  grain hypodermically being justified. Aminophyllin, 4 grains (0.24 Gm.) intravenously, is frequently attended by more prompt and greater relief than is morphine sulfate. It should be given slowly; if the pain recurs after a few hours it is permissible to repeat the dosage. Aminophyllin,  $1\frac{1}{2}$  grains (0.1 Gm.) by mouth three or more times a day, is recommended routinely in coronary thrombosis for an indefinite time.

Of the drugs, sedatives play an important part in the relief of painful discomfort over the heart, due to other forms of heart disease; or treatment of the primary conditions is indicated if other than cardiac in origin.

## 3. ABNORMAL RHYTHM OR RATE

From the standpoint of general practice the following arrhythmias are the most important as they can usually be recognized at the bedside and often are amenable to treatment; ventricular extrasystoles, auricular fibrillation, auricular flutter, paroxysmal auricular tachycardia, ventricular tachycardia and complete heart block. Extrasystoles unless frequent and accompanied by palpitation or precordial discomfort rarely call for treatment, but if so, sedatives should be first of the drugs used. Very rarely it may be necessary to use quinidine sulfate or digitalis in trying to stop them. The principles in giving these two drugs is the same here as on other occasions of their use, except usually smaller and less frequent doses are necessary. If the extrasystoles first appear while the patient is under digitalization they probably signify digitalis effect.

Auricular fibrillation and auricular flutter may be discussed together because two drugs are useful in both instances; namely, digitalis and quinidine sulfate. Digitalis is indicated in auricular fibrillation, unless perhaps in the case of "slow" fibrillation without congestive failure. Digitalis does not stop fibrillation but decreases the pulse deficit and the ventricular rate. All patients with auricular fibrillation should not be given quinidine sulfate, especially those with fibrillation of long standing. Quinidine sulfate is best indicated in the case of short duration, without congestive heart failure, and with a ventricular rate under 110. The auricular fibrillation of thyrogenic origin is especially suitable for quinidine sulfate therapy. Special caution is urged in the long-standing fibrillation with congestive failure of some duration, and quinidine sulfate will probably do no good anyway. Frequently it is advisable, especially in rapid fibrillation, to digitalize the patient before giving the quinidine sulfate. Digitalization and quinidine sulfate are advisable in auricular flutter and return to normal rhythm may be expected.

Quinidine sulfate should be given first in a test dose of 3 grains to note any untoward effects of susceptibility. If any serious toxic effect occurs it is likely to be one of respiratory failure and caffeine sodium benzoate, 15 grains, should be given intravenously immediately, and artificial respiration if neces-

sary. When the patient is known not to be susceptible, the quinidine sulfate may be given in 6-grain doses every four hours until rhythm is restored. Larger doses more frequently may be used if close observation and electrocardiographic control are available. Another often satisfactory clinical method is to give 3 doses a day, increasing the dose for each succeeding day by  $1\frac{1}{2}$  grains, as for example, 3 grains three times a day, then  $4\frac{1}{2}$  grains three times a day the next day, and so on. Usually it is not wise or necessary to give higher doses than  $10\frac{1}{2}$  or 12 grains three times a day.

If vagal or ocular pressure has not stopped an attack of paroxysmal tachycardia, three drugs may be considered: quinidine sulfate, digitalis, and acetyl- $\beta$ -methylcholine chloride (mecholin or mecholyl). The dosage of the acetyl- $\beta$ -methylcholine is 15 to 20 mg. subcutaneously. Atropine sulfate will counteract any untoward effect of the acetyl- $\beta$ -methylcholine. If attacks are frequent quinidine sulfate, 3 grains one to three times daily, may be useful in preventing recurrence. Sedatives are suggested also to relieve anxiety and promote rest.

Ventricular tachycardia is a dangerous arrhythmia and often responds satisfactorily to quinidine sulfate therapy, large doses and even intravenous use of quinidine sulfate being justified in some instances.

The drugs of use in complete heart block are epinephrine hydrochloride, ephedrine sulfate, barium chloride, and possibly atropine sulfate. Epinephrine hydrochloride, 5 to 15 minims of 1:1000 solution hypodermically or intracardiac, is used for the attack of Adams-Stokes syndrome, while ephedrine sulfate,  $\frac{3}{8}$  grain by mouth one to three times daily, may help in preventing severe and frequent attacks. Barium chloride,  $\frac{1}{2}$  grain by mouth, three or four times a day, is sometimes effective in preventing attacks.

## II. TREATMENT INDICATED BY ETIOLOGY

In rheumatic fever the salicylates still remain the therapeutic stand-by as far as drugs are concerned. The newly used drug, sulfanilamide (para-amino-benzene-sulfonamide, prontosil), offers some promise, but its effectiveness in rheumatic fever must await further observation. In hypertensive heart disease and coronary arteriosclerosis any drug therapy at



present is entirely for symptomatic relief. Thyrogenic heart disease is of two varieties, the so-called "myxedema heart" and thyrotoxic cardiac disturbances. When congestive failure appears, its management is the same as in other instances. Desiccated thyroid gland in sufficient quantity to correct the myxedema improves the heart condition providing arteriosclerosis and resultant myocardial changes are not too great, and these very features may in a way influence the amount of thyroid the patient can take without producing angina pectoris or other symptoms of too great cardiac activity in a heart long unaccustomed to it. In the thyrotoxic case iodine in some form is a part of the program for preoperative preparation. When syphilis is the etiology of cardiovascular disease, alone or with associated arteriosclerosis, arsenic, mercury, bismuth and the iodides in their various forms must be considered. More often the problem is one of syphilitic aortitis with or without aortic valvular disease rather than actual syphilis of the heart. By the time these cases have a predominant cardiac phase the matter of treatment is not so much specifically against the spirochete as against the damage it has caused. In such cases the arsenicals are used only after careful consideration of the individual case, then with caution. No effective drug treatment of subacute bacterial endocarditis (*Streptococcus viridans*) is known.



## CLINIC OF DR. GEORGE C. GRIFFITH

### PRESBYTERIAN HOSPITAL

#### DIET IN THE TREATMENT OF HEART DISEASE

THE intent of this paper is twofold: first, to show the purpose of diet regulation in heart disease; second, to give specific directions for diet management: (a) in organic heart disease prior to the onset of failure, (b) in congestive heart failure, (c) in the acute cardiac accidents, and (d) during the convalescent period.

Diet regulation in heart disease has but one purpose; *i. e.*, the *lessening of the work demand of the heart*. There are two ways by which this can be accomplished; first, by restricting the intake sufficiently to maintain normal weight and nutrition; and, second, by avoiding those foods which directly or indirectly stimulate the heart, and those foods which increase the work demand by prolonging or impairing the digestive process.

The nutrition of the body tissues, the weight of the body, and the etiologic factors causing the heart disease, must be considered when approaching the problem of lessening the work demand upon the heart. For example, weight reduction is often considered essential in cardiac management, because it is generally conceded that the sheer bulk of inert material increases the work demand of the heart. Under normal conditions of muscular development, there is a ratio of development maintained between the myocardium and the skeletal muscle; but this ratio is not true when weight increase results from the fat. There is no compensatory increase in the strength of the heart, and this organ is forced to labor under a serious handicap. Because of the discomfort to the obese patient from the circulatory embarrassment, lack of exercise

leads to further increase of weight, adding an additional burden on the heart.

Food restriction is of importance not only for the correction of obesity, but also because of the influence certain foods possess in increasing the work demand of the heart. The brilliant results which have been achieved in restoring compensation in a failing heart by thyroidectomy, give evidence of the extent to which we can lessen the work demand of the heart by slowing down the metabolic rate. A similar effect can be obtained, in some measure at least, by the restriction of protein, and thus reducing that stimulus to metabolism known as the specific dynamic action which comes from this important component of every diet. It is definitely demonstrated that protein foods cause an acceleration of surprising magnitude and duration; and that a meal of 50 Gm. of protein throws an extra burden of work on the heart equivalent in energy output to four hours of cardiac work under fasting conditions. With an impaired myocardium it is important to give a patient sufficient of this necessary food element, namely, protein, to meet nutritional needs; *i. e.*, approximately 0.6 Gm. per kilogram of body weight or about 50 Gm. per day for the average individual. This provides a margin of safety, but does not increase the specific dynamic action necessary to maintain nutritive needs, and the patient avoids the danger of an unduly accelerated metabolism. Proger proposed, therefore, to obtain the good results obtained by thyroidectomy by semistarvation, reducing the metabolism, the blood pressure and the pulse rate. Some surprising results have already been obtained.

Carbohydrate is the most readily utilizable fuel to furnish the contracting heart muscle the material to produce energy. Since a damaged heart is already laboring under a handicap, it should be furnished with this easily utilizable fuel in large amounts. Animal experimentation and clinical experience prove this assumption. It has been shown that the myocardium of dogs poisoned with the diphtheria toxin, which have gone into failure, is relieved by the intravenous injection of glucose more quickly and satisfactorily than by any other means. Clinical experience also indicates that sugars give a better and quicker stimulus to an exhausted muscle than any other food or medication.

Fats should be eliminated as far as possible from the diet. Fats burn in the flame of the carbohydrates; therefore, in the cardiac patient who is overweight he should be forced to burn up his own fats and at the same time preserve the integrity of his body tissues by giving the appropriate amount of protein and carbohydrate. Arteriosclerosis and coronary sclerosis may be retarded if we paid more attention to the utilization of fats. Therefore, I repeat again, fats should be eliminated as far as possible from the diet, protein given in amounts just sufficient to insure against nitrogen loss, and carbohydrate in sufficient quantities to meet the caloric needs of the patient.

Attention must be given to the intake of minerals, vitamins and salts. To provide minerals, small quantities of the leafy vegetables and milk should be included in the diet. Orange juice and tomato juice provide sufficient vitamins. Salt should not be completely eliminated, except where there is edema, so that in the patient who has not gone into congestive failure the average amount of salt cooked in vegetables should be allowed, reducing the amounts of sodium bicarbonate and sodium chloride intake beyond that used in the kitchen.

The diet should never be bulky, and small frequent meals are to be preferred to three large or bulky meals. A simple dessert at the end of a meal gives a sense of fulness and satisfaction, which often enables a patient to rest contented with a smaller quantity of food than otherwise would be the case. Glucose taken between the meals in the form of "dextrettes" or glucose "suckers," such as sour balls, provides the needed energy and prevents the mental and physical exhaustion of which cardiac patients so frequently complain.

The diet in the patient with hypertensive heart disease, coronary sclerosis and angina pectoris should be the same as the keynote of his life: "moderation in all things." That is, prior to congestive failure, the diet should be sufficiently broad to include all the food elements, simple, well-balanced, and definitely limited in amount. The following foods should be avoided because they produce flatulency, are indigestible and capable of producing gastro-intestinal disturbances:

- |   |  |
|---|--|
| 1. Beans, especially dried.             | 14. Nuts.                                |
| 2. Cabbage.                             | 15. Onions.                              |
| 3. Cheese.                              | 16. Pastry.                              |
| 4. Corn.                                | 17. Pork.                                |
| 5. Corned beef.                         | 18. Potted meats.                        |
| 6. Condiments (mustard, tabasco, etc.). | 19. Preserved and pickled fish and meat. |
| 7. Cucumbers.                           | 20. Radishes.                            |
| 8. Duck.                                | 21. Raisins.                             |
| 9. Garlic.                              | 22. Rich desserts.                       |
| 10. Goose.                              | 23. Salty foods.                         |
| 11. Green and red peppers.              | 24. Sausages.                            |
| 12. Meat broths (especially soups).     | 25. Stews, sauces and gravies.           |
| 13. Melons.                             |  |

Following the general rules laid down above, and omitting the articles enumerated, three sample menus are given, which have been found of value to the cardiac patient who should limit his diet because of hypertensive heart disease, arteriosclerosis, coronary sclerosis or angina pectoris:

#### *Menu No. 1*

- Breakfast: Sliced orange or orange juice.  
 Wheatena with skimmed milk and sugar.  
 Poached eggs on toast (2).  
 Glass of skimmed milk.
- Lunch: Vegetable platter with poached egg.  
 Endive salad with cottage cheese.  
 Chocolate-flavored junket.  
 Melba toast.
- Dinner: Boiled lamb.  
 New peas.  
 Buttered cauliflower.  
 Stewed celery.  
 Lettuce and tomato salad, without dressing.  
 Bread and butter.  
 Sliced peaches.  
 Glass of buttermilk.

#### *Menu No. 2*

- Breakfast: Sliced pineapple (canned or fresh).  
 Oatmeal with skimmed milk and sugar.  
 Soft boiled eggs (2).  
 Toast and butter.  
 Skimmed milk.

Lunch: Split pea soup (without meat stock).  
Spinach with poached egg.  
Sliced bananas.  
Bread and butter.

Dinner: Stewed chicken.  
String beans.  
Boiled rice.  
Carrots, buttered.  
Tomato stuffed with cottage cheese.  
Bread and butter.  
Fresh grapes or strawberries.  
Glass of buttermilk.

*Menu No. 3*

Breakfast: Stewed prunes or apricots.  
Cream of wheat with skimmed milk and sugar.  
Poached eggs (2).  
Toast and butter.  
Skimmed milk.

Lunch: Vegetable soup (made without meat stock).  
Sliced cold boiled chicken.  
Creamed asparagus on toast.  
Stewed plums.  
Bread and butter.  
Glass of buttermilk.

Dinner: Broiled fresh haddock.  
Creamed cauliflower.  
Baked eggplant.  
String beans.  
Endive and orange salad with no dressing.  
Bread and butter.  
Jello, with fresh fruit.  
Glass of buttermilk.

NOTE: Tea, coffee and alcohol may be utilized in accordance with the individual case.

In the presence of edema due to myocardial failure, the best diet to be instituted is that formulated by Karell. This diet accomplishes the threefold purpose for which it is intended, namely, limitation of fluids, low sodium chloride intake, and restriction of caloric intake. At the end of one week with the subsiding of the edema, the modified Karell diet should be instituted, as follows:

*Standard, or Strict Karell Diet:*

Eight hundred cc. of milk is given daily, 200 cc. taken at each of the following feedings: 8 A. M., 12 noon, 4 P. M., and 8 P. M. This amount of milk will furnish

Protein . . . . .	26	Gm.
Carbohydrates . . . . .	40	Gm.
Fat . . . . .	32	Gm.
Sodium chloride . . . . .	1.6	Gm.
Water . . . . .	796	cc.
Total calories . . . . .	552	cc.

The above dietary is maintained for a period of one week, after which the modified diet is instituted, as follows:

*Modification of the Karell Diet:*

Eighth day:

Milk, 800 cc., in four feedings of 200 cc. each. This may be given at 7.30 A. M., 12 noon, 4.30 P. M., and 9 P. M. Or, it may be given at 8 A. M., 12 noon, 4 P. M., and 8 P. M.  
10.00 A. M.: 1 soft-cooked egg and 1 slice of toast.

Ninth day:

Milk, 800 cc., in four feedings (part of this may be made into junket, ice cream, and part in milk-soup if desired).  
10.00 A. M.: 1 egg and 1 slice of toast.  
12.30 P. M.: Milk-soup.  
4.30 P. M.: 200 cc. of milk, 1 slice of toast.  
8.00 or 9.00 P. M.: Milk, 200 cc.

Tenth to twelfth day:

Milk, 800 cc., 2 eggs, 2 slices of toast, 100 Gm. of cooked rice; one serving of asparagus, celery, cauliflower or carrots, prepared and distributed as described above.

Thirteenth to fifteenth day:

7.30 A. M.: 150 cc. of milk, 1 soft-cooked egg, 1 slice of toast, very little butter.

Noon: 1 poached egg on 1 slice of toast.  
100 Gm. of rice (well cooked and butter lightly); 150 cc. of milk: custard (made of 150 cc. of milk, 1 egg, <sup>1</sup>/<sub>2</sub> teaspoonful sugar).

4.30 P. M.: Soup (made of one serving of asparagus, celery or carrot, and puréed into 150 cc. of milk, seasoned with butter and dash of salt).

<sup>1</sup>/<sub>2</sub> = well-baked apple.

150 cc. of milk.

9.00 P. M.: 200 cc. of warm milk.



# DIET IN THE TREATMENT OF HEART DISEASE 1001

Sixteenth to eighteenth day:

7.30 A. M.: 50 Gm. of boiled rice with 50 cc. of milk.

1 egg, soft-cooked, 1 slice of toast, buttered.

150 cc. of milk.

Noon: One serving of asparagus, creamed with 50 cc. of milk and butter, served on one slice of toast, 30 Gm. of baked potato, with butter.

150 cc. of milk.

4.30 P. M.: 50 Gm. of boiled rice, 50 cc. of milk, 1 pat of butter.

1 baked apple with custard made of 1 egg and 50 cc. of milk.

150 cc. of milk.

9.00 P. M.: 150 cc. of warm milk.

Nineteenth to twenty-first day:

7.30 A. M.: 60 Gm. of cooked oatmeal.

1 soft-boiled egg.

1 slice of toast.

200 cc. of milk.

10 Gm. of butter.

Noon: 30 Gm. of baked potato; 1 pat of butter.

100 Gm. of boiled rice.

1 egg.

100 cc. of milk made into pudding of any type.

150 cc. of milk.

1 serving of stewed celery.

4.30 P. M.: 30 Gm. of baked potato, puréed with 100 cc. of milk.

1 pat of butter.

1 soft-cooked egg.

9.00 P. M.: 1 slice of toast.

1 baked apple.

150 cc. of milk.

In those few patients who have a definite milk intolerance, a diet similar to the following should be used to replace the strict Karel diet for the first seven days of treatment:

## Nonmilk—800 cc. Fluid Diet:

8.00 A. M.: 200 Gm. of barley gruel made with water, and seasoned with butter.

1 soft-cooked egg.

1 slice of dry toast.

Noon: 200 Gm. of potato purée, made with water and seasoned with butter.

Zwieback.

Baked egg.

4.00 P. M.: 200 Gm. of oatmeal gruel, made with water, and seasoned with butter.

1 slice of dry toast.

8.00 P. M.: 200 Gm. of potato purée, made with water and seasoned with butter.

Zwieback.

The Karell diet and its modifications are relatively severe, but the patient usually cooperates well when he notes the rapid disappearance of the edema. Cracked ice may be used to alleviate the thirst if the water is expectorated. Chewing of gum helps to avoid thirst, and the sucking of lemon sour balls not only relieves thirst, but also gives a readily available supply of glucose. I frequently place patients with recurring edema on the Karell diet one day or two days of each week, with much benefit. Where there is edema from other causes, such as orthostatic varicosities, postphlebitis, pregnancy, hepatic cirrhosis, or abdominal malignancy with ascites, benefit may be obtained from the use of the Karell diet.

In the acute cardiac accidents, such as acute coronary thrombosis, stab wounds of the heart, and contusions of the heart, the diet should be regulated to decrease the work demand of the heart. The Karell diet as outlined above may be used, or the diet advocated by Sir Thomas Lewis, as follows:

*800 Calorie Diet, to be Used for Five Days:*

8.30 A. M.: (a) Toast, 1 slice, with honey.

1 cup of tea, with two lumps of sugar.

or

(b) 1 raw egg in 6 ounces of milk.

1.30 P. M.: Minced chicken, 2 ounces.

Bread, 1½ ounces.

7.00 P. M.: (a) Custard, 5 ounces.

or

(b) Milk pudding, 4 ounces.

or

(c) Bread and milk (milk, 4 ounces; bread, 1 ounce, with a little sugar added).

Fluids should be tea or milk, and not to exceed 20 ounces, and to be taken between meals.

In conclusion, the character of the diet will not alter the course of the disease; but its well thought-out and considered

restriction will increase cardiac efficiency by relieving the heart of unnecessary effort, and will thus bring comfort to the patient and prolong his life. The rules worth following in the dietary regulation of the cardiac patient should be: (1) the maintenance of a normal weight and tissue nutrition, (2) a limited amount of protein, and (3) a liberal amount of carbohydrate.



## CLINIC OF DR. T. GRIER MILLER

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### THE ACUTE ABDOMEN AND THE GENERAL PRACTITIONER

I SHALL discuss a series of cases illustrative of the acute abdomen as encountered by the general practitioner. Surgeons usually talk about the acute abdomen, and properly so because it is one of their most puzzling problems and a problem which often they must solve without the help of various highly developed diagnostic procedures. In the presence of an acute suppurative appendicitis, an acute pancreatitis, a perforated duodenal ulcer or an ectopic pregnancy no time is available for elaborate roentgenologic studies, for chemical investigations of the blood, for a trial of some conservative medical regimen or even, not infrequently, for consultation with an internist. Consequently, the surgeons have become expert in recognizing, on clinical grounds alone, the cases in which operative therapy is indicated and those in which it is contraindicated. That decision is a most important one to make, and sometimes the only one that can be made, but unless, under the circumstances of each case, one has clearly in mind, as his ultimate goal, the determination of an exact diagnosis, he fails in his professional obligation.

Upon the general practitioner devolves the problem of selecting the cases that he shall have the surgeon see. Many of the cases with acute abdominal symptoms are not of a surgical nature and frequently, unless he believes them so to be, he is not justified in calling for surgical assistance: to do so under some circumstances may defeat the chief therapeutic indication, that of reassuring and putting at ease a distressed mind. Furthermore, to call a consultant, either internist or

surgeon, may impose an unnecessary financial burden or delay effective and prompt medical therapy.

It is necessary, therefore, that the general practitioner himself understand the acute abdomen and especially the disturbances that lead to it. This, in all fairness, the competent practitioner does understand, and often better than the average specially trained internist or surgeon because he has more frequent contact with it and because usually he is in possession of facts about the patient's past medical, family and social history, facts often that cannot be elicited by questions at a time of stress.

I shall attempt, therefore, to present the subject from a broader viewpoint than that of the person whose work is limited to any special field of medical endeavor. I shall not refer to the typical case of acute appendicitis, to the "frozen attitude" of the young man who falls on the street with the violent abdominal pain of a perforated duodenal ulcer or to the amenorrheic young woman who suddenly develops the phenomena of intraperitoneal hemorrhage, but rather to certain of the more confusing cases that I have encountered. In so doing I am selecting from my personal experience cases that originally at least presented a real problem in diagnosis and in some instances were correctly diagnosed only at operation or autopsy. A consideration of such cases should serve at least to develop in each of us a feeling of humility and caution in approaching every instance of the acute abdomen and always of erring, if one must do so, on the side of greatest safety for the patient, even if it involve a needless operation.

It may be objected that the cases I am about to present represent the rarer and more complicated instances of the acute abdomen and that they occur more frequently in the experience of the surgeon and medical consultant than of the general practitioner. To this I can reply only that such cases, at their onset, are encountered by the family physician and that, unless he appreciates their potentialities and acts on such a basis, the internist and surgeon will not see many of the cases when special therapy is still available.

Acute appendicitis, it must be admitted, is the most common and at the same time the most confusing of all the abdominal lesions that produce the acute abdomen. Every fourth

year medical student can diagnose the typical case, but one cannot practice medicine for long without appreciating that many cases present at first clinical phenomena that defy the classical picture: a misleading history, left-sided or upper abdominal pain or little pain anywhere, tenderness elsewhere than over McBurney's point, no gastric disturbance, no fever or increase of pulse rate, no leukocytosis. No one symptom or sign is diagnostic in all cases.

**Case I.**—I have today seen with one of our surgeons a patient, a man of forty, with a negative previous history, who along with his son developed abdominal pain two days ago and attributed it to oysters which they had eaten the preceding evening. The son recovered after an enema but the father continued to have generalized abdominal pain and marked distention, but no nausea or vomiting and free bowel action. Although he had generalized abdominal pain and tenderness, it was most marked in the left lower quadrant. One was tempted to think that he too had an acute enteritis, but he had a fever of  $99.4^{\circ}$  F., a pulse rate of 136 and rectal examination revealed tenderness in the midline of the pelvic basin. Operation disclosed that he had an acute appendiceal inflammation, the tip of the appendix being in the pelvis, with free fluid in the abdomen.

Such cases as this one are frequently encountered by the general practitioner and unless he bears constantly in mind the possibility of an atypical appendicitis, no matter what the character of the acute abdominal symptoms, an error in diagnosis or at least an unnecessary delay in diagnosis is likely to occur. Had we waited even for a few hours to secure typical localizing signs in this case the situation would have been much more serious and the chances of a fatal outcome greatly increased. No doubt this patient, like his son, did have an acute enteritis, sufficient to explain his loose stools, but, as a complication of that process, he developed an acute appendicitis. The latter might easily have been overlooked.

**Case II.**—Another patient, No. 2294, a woman of seventy-five, who had repeated gallstone attacks with jaundice and who was considered inoperable because of myocardial disease, de-

veloped in one attack localized tenderness and rigidity in the lower right quadrant of the abdomen with fever. Operation disclosed an appendiceal abscess. Her convalescence was satisfactory, but two years later she developed a watery diarrhea, nausea and vomiting without definite pain or distention. This was not diagnosed promptly but after three days the typical picture of intestinal obstruction developed and at operation it was found that a knuckle of bowel had been clamped off by an adhesive band in the appendiceal area. She died as a result.

In this case, although a previous appendectomy should have suggested the possibility of adhesive bands producing intestinal obstruction, I was misled by the previous history of gallstone attacks and by the diarrhea. More prompt hospitalization and consultation with a more experienced clinician would possibly have led to earlier recognition of the lesion and have saved the patient's life. In any event the experience has been a valuable one and has induced me on a number of occasions subsequently to suspect intestinal obstruction early and to act accordingly.

One not infrequently encounters a case in which the symptoms and signs seem to indicate an acute or subacute appendicitis, although at operation the appendix is normal. In the case detailed below it was only after a number of weeks following operation that a constricted and inflamed right ureter, believed to be the cause of the symptoms, was discovered.

**Case III.**—No. 4457, female, aged twenty-eight, the mother of three children, came in with a story of sharp pains in the lower right abdomen and slight fever for a week. Examination disclosed considerable tenderness deep in the appendiceal area, just above the brim of the pelvis. No superficial tenderness or rigidity was demonstrable. The leukocytes numbered 9100. A barium enema revealed a spastic cecum and tenderness about the base of a well-filled appendix. Urinalysis was negative and the basal metabolic rate was normal. Pelvic examination was reported as negative.

Although it was appreciated that the appendix might not be responsible, it was finally decided, after six days' observation, during which time the leukocytes had reached 10,600 and the temperature on a number of occasions 99.4° F., to ex-



plore the lower right abdomen. The appendix was not obviously diseased but it contained several fecaliths and a small hard nodule was found in its mesentery; it and the nodule were removed. The pelvic organs were normal to palpation and no other lesion was discovered. The appendix was found, on microscopic study, to be the seat of some chronic inflammation and the nodule to be due to chronic lymphadenitis.

Her pains persisted, grew more severe, she continued irregularly to be febrile, and finally a pelvic examination by another gynecologist revealed tenderness immediately over the lower right ureter. A urogram indicated some obstruction at that point and a cystoscopic examination showed evidence of a right-sided ureteritis. The introduction of a ureteral catheter reproduced the characteristic pain.

The diagnostic error made in this instance is perhaps excusable, especially in view of the reported negative pelvic examination and the negative urinalysis, but it serves to illustrate the care that should be exercised in the study of each case before operative interference. The subsequent course of the case has been such as to suggest that even the diagnosis of ureteritis may have been unjustified; treatment for that lesion led only to an increase of symptoms and cure was not obtained until after a prolonged course of psychotherapy. The latter incidentally involved the rationalization of many psychic traumas suffered in childhood. It is this aspect of a case that is often better understood by the family physician than by the so-called "specialist."

An acute cholecystic attack, although usually easily diagnosed, may also present clinical phenomena that defy prompt analysis.

**Case IV.**—No. 3458, male, a surgeon, fifty-two years of age, had suffered repeated attacks diagnosed left renal colic and after a fall on a golf course had developed severe epigastric pain with tenderness over the ensiform process. Soon the pain shifted to the right back, he had difficulty in breathing, a temperature of 100.4° F. and a leukocytosis of 13,400, later 24,000. Although at that time he had, in addition, some pain and tenderness in the gallbladder area his right diaphragm was fixed, expansion of the right chest was restricted, breath

sounds were faint and râles were heard. A right basal pneumonia was suspected and operation was withheld. Then he developed moderate jaundice, had an indirect van den Bergh reading of 3.2 units and no signs of consolidation appeared. Although repeated roentgenologic studies indicated some mediastinal reaction and a questionable lesion at the right pulmonary base, these cleared up satisfactorily and a Graham-Cole roentgenologic study showed no gallbladder shadow. The fact that his primary lesion on that occasion was an acute cholecystitis is indicated by the fact that two years later he had a similar attack, again with widening of the mediastinal shadow and fluid in the right pleural cavity (demonstrated by paracentesis). In spite of the signs of chest disease his abdomen was then explored by Dr. E. L. Eliason who found a perforated gallbladder containing stones and a subdiaphragmatic abscess. Following drainage of the gallbladder and the abscess he made a good recovery, but four months later reoperation was necessary for a common duct stone; at the same time the gallbladder was removed. He has had no symptoms during the three years that have elapsed since that time.

This case illustrates how a complication may obscure the symptoms and signs of the primary and more important lesion. Undoubtedly in his original attack this patient had an acute suppurative gallbladder superimposed upon a chronic calculous cholecystitis, later with extension of the inflammation up over the liver and through the diaphragm and finally a nonsuppurative mediastinitis. Whether or not operative interference at the time of the original attack was indicated is open to question, but the case serves to illustrate an acute abdomen due to a complicated situation, one that defies the best efforts of the internist and the surgeon as well as the general practitioner.

The value of roentgenologic study of the gallbladder is emphasized in the following case, one in which the original diagnosis was correct but in which subsequent events, with the exception of the Graham-Cole test, seemed to disprove that diagnosis.

**Case V.**—No. 4628, male, aged thirty-nine, with a previously negative history, developed during the night a severe pain in the right upper quadrant of the abdomen. When I

saw him a few hours later, marked tenderness over the gallbladder area was observed and the location and severity of the pain led to a diagnosis of cholelithiasis and morphine was administered. During the next five days he had several recurrences of the painful attack and became jaundiced. Finally he had an attack in which the gallbladder could be easily palpated, but the tender mass and the pain disappeared after morphine. Subsequently his symptoms disappeared completely and it was then learned that his friends had noted some jaundice for several weeks before his original attack. That item of history, together with the sudden enlargement and quick disappearance of the gallbladder mass, led to conservative therapy, and after about two weeks all the symptoms and signs of disease had disappeared.

At that stage it was suspected that the original diagnosis of gallstones was in error and that he had had only an acute catarrhal jaundice with common duct obstruction. Biliary drainage showed good gallbladder concentration but a roentgenological study revealed a single large gallstone (a negative shadow). Because of that observation, and in spite of his history of painless jaundice preceding the painful attacks, operation by Dr. E. L. Eliason disclosed a single stone embedded in the wall of the ampulla of the gallbladder. He has been entirely well since the operation.

This case illustrates the importance of making every possible study in order to arrive at a correct diagnosis. Although the history, the physical signs and the biliary drainage results seemed consistent with the diagnosis of acute catarrhal jaundice, and one might have gone no further in his study of the case because for the time being the patient was symptom-free, the roentgenologic investigation gave immediately a positive diagnosis of cholelithiasis and indicated surgical therapy. I believe that every case of so-called "acute catarrhal jaundice" should subsequently have a biliary drainage and a cholecystogram. Many of these cases eventually come to operation for gallstones.

As an illustration of an acute abdomen, at least in its demand for prompt and effective therapy, I now cite a case of urinary bladder obstruction that was at first looked upon as an instance of indigestion on a cardiac basis.

**Case VI.**—No. 903, male, aged seventy-five, who had been under my observation twelve years previously because of nervous symptoms and some frequency of urination, consulted me again in February, 1934, with the following story. For several months he had been having cardiac symptoms and he had finally, two weeks previously, gone to Atlantic City, under a physician's orders, for a rest. Immediately he had developed marked nausea and vomiting, could not take food or even water without vomiting. None of the measures for the control of his indigestion prescribed by a local physician had been of any benefit.

He looked worn and distressed, was pallid and very restless and talked hesitatingly and with difficulty in finding the proper words. I noted an ammoniacal odor on his breath and found his lower abdomen distended and dull to percussion. He voided some urine but without effect on the cystic lower abdominal mass. The urine was negative but for a low specific gravity (1.008). Prostate was only moderately enlarged. At the same time, because of the general state of the patient and the large mass, suggestive of a markedly distended bladder, I took blood for the determination of its urea nitrogen content. That proved to be 64 mg. per cent.

He was immediately hospitalized and his urinary bladder decompressed. Two days later his urea nitrogen concentration was still 63 mg. per cent, but within two weeks this figure was practically normal and Dr. Alexander Randall then was able to remove a part of the median lobe of his prostate by the electric method. He made a good convalescence and by May, 1934, his urea nitrogen was 14 mg. per cent. He has had no further cardiac, digestive or urinary tract symptoms.

Coronary thrombosis, especially of the posterior branch, may present a clinical picture suggestive of an acute digestive disturbance. I have had the following distressing experience.

**Case VII.**—No. 1030, female, aged forty-five, for about five years, following the cessation of menstruation, had had, in addition to hot flushes and sweats, a distinct tendency to adiposity, a moderate increase in blood pressure and attacks

of urticaria. In 1934 she developed pain in the feet on walking, which special tests by Dr. Lewis H. Hitzrot seemed to indicate were on a basis of vascular spasm; no organic vascular lesions could be demonstrated. Soon her blood pressure had reached 180/120, but clinical examination of the heart and urinalyses were negative. Blood studies were negative.

One evening, while sitting quietly at her home, she developed suddenly epigastric pain, which her husband, a physician, believed to be on a digestive basis. She took some codeine and the next morning felt well except for a feeling of fulness in the abdomen. She had a colon irrigation in the afternoon and felt relieved, though the abdomen was still somewhat distended and she was slightly nauseated. She was able to go out for a walk that afternoon, but soon after returning home she developed a violent pain beneath the sternum with radiation into the lower jaws. Then, for the first time, a coronary lesion was suspected and electrocardiographic study indicated that she had a posterior wall infarct. Subsequently she developed pulmonary and cerebral infarctions from which she died.

This case is also interesting in that the patient had previously demonstrable evidence of peripheral vascular disease and that such disease came on with the onset of her menopause and was associated with vascular hypertension. Thus it suggests a coronary rather than a myocardial explanation for some of the cardiac symptoms of menopausal hypertension. In any event this case serves to emphasize what is already well known, that coronary occlusion may mimic the symptoms of a digestive disorder.

Rupture of the thoracic aorta is an unusual occurrence, but, in addition to the case which I shall now report, I have seen the autopsy specimens of a similar case which was presented in a clinical-pathologic seminar at the Presbyterian Hospital in New York. Both cases had a history indicative of an upper abdominal catastrophe, such as an acute pancreatitis or a ruptured duodenal ulcer.

**Case VIII.**—No. 957, male, aged fifty-five, had been under my general observation for fourteen years. He had had headaches all his life and for more than twenty years he had had

digestive symptoms, but all studies had failed to reveal any organic disease. Blood pressure, urinalysis, blood counts and Wassermann test had always been negative.

At 11.20 A. M. on the morning of June 5, 1929, while swimming in an indoor pool, he developed a sharp pain in the epigastrium. He was able to get out of the pool, dress himself and come to my office. I found him ashen gray in color and obviously suffering greatly. The pain by this time was both epigastric and lumbosacral. The upper recti seemed resistant, but there was no boardlike rigidity. The upper abdomen was tender, especially on the right side. A perforated ulcer or an acute pancreatitis was immediately suspected and he was promptly taken to the University Hospital. While undressing he developed a sudden exacerbation of the pain and fifteen minutes later another such attack. His leukocytes numbered 20,400. He was given morphine and scopolamine. The next morning his temperature was but 99° F. and his pulse rate 88, but he had 21,000 leukocytes. Dr. John B. Deaver thought he had an acute pancreatitis with hemorrhage into that organ. Two hours later he died suddenly and an autopsy revealed an unsuspected rupture of the lower thoracic aorta.

As representative of the abdominal crises of *tabes dorsalis*, I present a case that fortunately was recognized and that did not undergo the various operative procedures that are so frequently reported in that disease. It is only fair to say, however, that in this instance, had the diagnosis of *tabes* not been made in advance and the typical physical signs sought for, operative therapy might have been considered for the severe abdominal pains.

**Case IX.**—No. 3911, male, fifty-eight years of age, complained of irregular seizures of gnawing abdominal pain, chiefly in the epigastrium. In addition he had regularly a sense of heaviness in the epigastrium after meals and much flatulence. Extensive studies of the digestive tract, including complete roentgenologic investigation, were negative but for spasm of the colon in the splenic area.

Careful inquiry into his history then disclosed that at the age of thirty he had a suspicious primary syphilitic lesion and on neurologic investigation it was found that he had Argyll

Robertson pupils, diminished patellar and Achilles reflexes and possible ptosis of the eyelids. On the basis of these observations a diagnosis of tabes was made and intensive antiluetic therapy after a few years brought about a complete disappearance of the abdominal attacks.

Finally, I wish briefly to outline the data obtained in our wards on a patient who was proved eventually to have polycystic kidney disease. This is an unusual lesion to associate with an acute abdomen, but the superimposed renal infection, a pyelonephritis, which accounted for the patient's original symptoms, not infrequently, like pyelitis, causes acute abdominal distress. The case should emphasize the importance regularly of making a careful microscopic study of the urine, as well as a general physical examination, in every case of the acute abdomen.

**Case X.**—No. 35-21807, a married woman of forty-nine years, was admitted to one of our surgical wards on December 29, 1935, for what was believed by her family physician to be an attack of acute appendicitis. Two days previously she had developed a sharp pain in the lower right quadrant of the abdomen with associated pain in the right flank and chilly sensations. Because of marked tenderness in the costovertebral angles, as well as in the right upper and lower quadrants of the abdomen, the presence of a mass in the right upper abdomen, a temperature of 104° F. and much pus in the urine, the diagnosis of appendicitis was considered inadequate and some renal lesion was suspected. A flat roentgenologic film showed shadows in both kidney areas that suggested the possibility of polycystic kidney disease. She was transferred to one of our wards two days after admission and further studies confirmed that diagnosis. Cystoscopic investigation revealed cystitis and evidence of infection in both kidneys. A pyelogram showed enlarged kidney pelves, probably due to polycystic disease; a urogram confirmed this. Urea nitrogen concentration was 19 mg. per cent but phthalein elimination for a two-hour period was only 25 per cent. Her fever subsided and leukocytes dropped to normal, but she still showed pyuria on discharge January 26, 1936.

She was readmitted on August 31, 1936, after another at-

tack of right upper quadrant pain with bloody urine. Masses were then easily palpable in the kidney areas, the urea nitrogen concentration was 118 mg. per cent and the phthalein output was only 5 per cent. Uremia led to her death on September 15 and autopsy confirmed the diagnosis of polycystic kidney disease with acute pyelonephritis.

These references to specific cases by no means cover the lesions responsible for the acute abdomen. One has only to think of acute pancreatitis, of ruptured duodenal or gastric ulcer, of traumatic lesions, such as a rupture of the liver or spleen, of certain intoxications, of mesenteric thrombosis, of brain tumor, of migraine, of acute enterocolitis, of intercostal neuralgia, so-called, and, especially in children, of rheumatism, to realize that I have barely approached the subject. Every physician, be he general practitioner, internist or surgeon, must constantly have all of these possible lesions in mind when he encounters the acute abdomen.



## CLINIC OF DR. H. L. BOCKUS

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### THE IRRITABLE COLON: DIAGNOSIS AND TREATMENT

It is possible to segregate from the functional disorders of the colon a group of cases having in common a disturbance of the neuromuscular mechanism of the bowel for which there is no organic cause, such as colonic disease, parasites, anomalies or disease outside the colon causing reflex symptoms. Formerly many of these cases were designated as spastic colon, mucous colitis and chronic colonospasm. These appellations are gradually being discarded. A diagnosis of colitis should be reserved for cases of primary inflammation of the colon. The neuromuscular disturbances are not always associated with increased tonus and shortening of the circular or longitudinal muscle fibers. Some instances of extreme atony must be included in the same general category of the neurogenic colonopathies. Consequently, the terms "irritable colon" (Jordan and Kiefer) and "unstable colon" (Kantor) are now being applied to this group of cases. Hurst has recently discussed the functional colonic disturbances under the title of the "unhappy colon." Possibly a clearer concept of the syndrome would be had if the whole group was designated as follows (Bockus and Willard):

#### COLONIC NEUROSES—IRRITABLE AND UNSTABLE COLON

1. Motor neurosis—disturbances of tone or peristalsis—including colonospasm, atony and nervous or emotional diarrhea.
2. Secretory neurosis—increase (mucous colitis) or diminution in the secretion of the mucous glands.
3. Mixed neurosis—characterized by dysfunction of both the motor and secretory mechanism. This classification serves to emphasize the protean character of the functional dis-

turbances of the colon, all of which depend upon an underlying lack of balance of the vegetative nervous system. Motor disturbances are more commonly encountered clinically. The mixed neuroses are next in frequency. The pure secretory disturbances are quite uncommon in the absence of concomitant spastic phenomena. The same patient may manifest any type of secretory or motor dysfunction at different times so that for clinical purposes a diagnosis of colonic neurosis, irritable or unstable colon is sufficiently accurate.

**Etiology.**—We cannot discuss in detail the various etiologic factors which can account for this syndrome. Any mechanism capable of influencing the vegetative nerve supply to the large bowel may be responsible. No one questions the importance of the psyche in many instances. A colonic neurosis is a civilization disorder. It is more commonly encountered in the more emotional races (Jews and Latins) and among emotional and so-called “temperamental stock.” Females are more frequently affected. Emotional or nervous stress and strain is often provocative of attacks in susceptible people. Although the psychic factor is often dominant, it is by no means universal. The underlying autonomic disturbance probably depends upon dysfunction of one or several units of the endocrine system. Both hyper- and hypofunction of the thyroid are frequently accompanied by “irritable” colon symptoms. Symptoms are commonly related to menstrual function. Ovarian dysfunction is noted in a high percentage of female patients with a colonic neurosis. There can be no question of the influence exerted by the pituitary, adrenals and the internal secretion of the pancreas on the abdominal sympathetic system. A fertile field for investigation remains to be explored in this realm of endocrinology. Allergic states unquestionably account for the initiation of irritable colon symptoms in many instances so that a great many factors, both exogenous and endogenous, must be considered in a careful survey on patients considered to be allergic. Many writers consider primary infection of the colon and simple constipation (habit type) as causes for the development of symptoms of colonic irritability. Cases of this type should be excluded from the “irritable colon” family and given their true designation of catarrhal colitis or simple constipation or dyschesia.

As a rule symptoms of colonic irritability do not occur in simple constipation until laxatives, cathartics, enemas or colon irrigations have been used for a long period of time. These symptoms depend upon an actual colitis and will disappear upon withdrawal of the offending agent unless the constipation was primarily due to an underlying neuromuscular dysfunction.

**Diagnosis.**—Symptoms attributed to the colonic neuroses comprise from 15 to 45 per cent of visits to internists interested in digestive tract disorders. Surely, this high incidence constitutes in itself a sufficient plea for a thorough understanding of the condition by every internist and surgeon. A long history of recurring bouts of abdominal discomfort related to or associated with irregular bowel habit constitutes the presenting complaint in most instances. The pain may be anywhere in the abdomen but is more often experienced in the lower quadrants, usually the lower left. It may be severe or mild but is commonly crampy and described as a feeling of "gas." Constipation or diarrhea may be present but at any rate the abdominal discomfort is often influenced by the act of defecation or expulsion of gas. A diagnosis of the "functional colon" must be made by exclusion. First of all, one must eliminate organic colonic disease, such as neoplasm, diverticulosis, bowel obstruction, dysentery, tuberculosis, ulcerative colitis or polyposis. A diagnosis of organic disease of the colon can usually be made without difficulty after physical examination, fecal analysis, proctosigmoidoscopy, rectal and roentgenologic examinations. If organic disease of the colon can be reasonably ruled out, consideration must be given to extracolonic diseases, which can reflexly disturb the function of the colon. Appendicitis, renal calculus, pyelitis, and pelvic inflammatory disease are common offenders but are rarely active over such long periods as the colonic neuroses. They are, of course, more prone to show signs of sepsis, fever and leukocytosis. However, in some cases the diagnosis will not be easy. A previous attack of appendicitis or pelvic inflammatory disease is at times followed by mechanical disturbances, which may induce symptoms quite similar to a true colonic neurosis. Nevertheless, entirely too many operations have been performed for the relief of irritable colon symptoms with the mis-

taken diagnosis of recurring appendicitis or some other acute intra-abdominal lesion. In the absence of symptoms and signs of acute appendicitis, laparotomy should always be postponed until a thorough investigation has been carried out and a trial on "irritable colon" management instituted. Recurring spells of diarrhea unassociated with the passage of pus or blood in the stools is frequently due to a "colonic neurosis," particularly if abdominal crampy pain is present. However, achlorhydria must always be considered, as it is a not uncommon finding in patients with the irritable colon. Symptoms of colonic dysfunction are often influenced by this gastrogenous factor and the administration of hydrochloric acid may bring about relief of the diarrhea and improvement in pain. A true gastrogenous achlorhydric diarrhea in the absence of an irritable colon rarely gives rise to abdominal pain preceding evacuation. Many other abdominal lesions and certain constitutional maladies, such as sprue and tuberculosis as well as lesions of the central nervous system may initiate an irritable colon syndrome. Almost any type of deficiency disorder may give rise to diarrhea or other manifestations of colonic dysfunction, which cannot always be differentiated from a true colonic neurosis. Indeed one occasionally encounters patients with a deficiency disorder induced by dietary restrictions imposed for the relief of colonic symptoms.

Granting the exclusion of all extraneous causes of colonic dysfunction, what are the criteria for the diagnosis of a true colonic neurosis? The *history* of the relationship of the abdominal discomfort to bowel evacuation in an individual with a disturbance of bowel habit is of paramount importance. The linking up of symptoms to evidence of psychic or vegetative imbalance is equally significant. Clinical evidence of an endocrine disturbance or allergy lends further support to the possibility of an irritable colon. The *physical examination* may reveal nothing abnormal with the exception of tenderness over the pelvic colon which may be stiff and narrow or lumpy due to scybala. I cannot refrain from sounding a word of warning concerning the possibility of a parietal abdominal neuralgia (Carnett) to account for pain of undetermined origin in one of the abdominal quadrants. One should hesitate about attributing pain which is constant for weeks or months to an irritable

colon even though a diagnosis of irritable colon is tenable for other reasons. Abdominal neuralgia and irritable colon commonly coexist in the same individual but treatment for the latter cannot be expected to influence the neuralgic type of pain. In my experience the superficial tenderness which is elicited by pinching a fold of skin and fat or making firm pressure on the abdominal wall made tense by straining is commonly due to postural strain, spinal curvature or spinal arthritis. This type of tenderness is frequent in patients complaining of a constant pain not influenced by bowel evacuation. Tenderness dependent upon colonic spasm is usually deep and elicited only when pressure is made directly over the colon (see Case II). The third aid in the diagnosis of the irritable colon is the *analysis of the feces*, too frequently neglected. The shape of the stool before or during attacks is often abnormal. It may be pencil shaped, flattened or scybalous. Clear, so-called "neurogenic mucus" may be seen on the outside of the movement in some cases. The stools may be mushy or even liquid for long or short periods of time. In a negative way the absence of gross or occult blood, pus and parasites is of importance. The *sigmoidoscope* is of great help in the diagnosis. Primarily it will assist in excluding the organic colitides and new growths, both of which commonly occur in the lower 10 inches of the bowel. In patients with the irritable colon, great difficulty is often experienced when the instrument is being introduced into the sigmoid. Severe pain in the lower abdomen is not infrequently due to the marked spasm of the musculature of the sigmoid. The ability to reproduce pain similar to the patient's chief complaint by manipulation of the instrument or the introduction of air into the bowel is a rather common experience. A clear, "non-inflammatory" type of mucus may be encountered within the lumen of the bowel.

A properly executed *roentgenologic study* of the colon is essential. An ordinary opaque enema will suffice in many cases but may need to be supplemented in others by a double contrast barium and air enema or by a progress meal study. First consideration must be given to the ruling out of organic disease, particularly in that portion beyond the reach of the sigmoidoscope. The opaque enema should be introduced very slowly

at body temperature and its rate of flow into the colon noted. In some cases of irritable colon the barium will be observed to pass up the lumen of the colon very rapidly. This is an indication of extreme irritability. The introduction of barium, even when given slowly, may produce subjective pain quite similar to the abdominal pain for which a physician's aid is sought. The silhouette of the filled colon will obviously be quite variable in different cases, and not infrequently change



Fig. 59.—Combining the features of extreme narrowing of the left colon and zonal span. Marked contractions are noted in 3 areas, the sigmoid, the midtransverse colon and the cecum. The symptoms were severe and closely simulated, at times, acute appendicitis.

considerably from time to time in the same patient. It can be markedly changed by the addition of more barium or by the expulsion of some of the barium contents into the ileum. Abnormal narrowing of some colonic segment, more particularly the left, is a common type of abnormality. Another less frequent finding is segmentive or zonal spasm. It is more often seen in the sigmoid and descending colon (Fig. 59). A deep-cutting contracture of spastic nature confined to the proximal

ascending colon is usually dependent upon some type of local disease in the vicinity, such as tuberculosis, malignancy, appendicitis or other mucosal disease. A considerable number of irritable colon cases show the fine, shallow, irregularly arranged, saw-tooth type of colonic margin described by Spriggs and Marxer as prediverticulosis (Figs. 62, 63). Haustral markings may be grossly exaggerated, markedly irregular or totally absent and all variations in between will be encountered. A markedly dilated atonic bowel may at times depend upon a primary neuromuscular disturbance or it may develop secondary to long-standing dyschesia. In extreme irritability of the colon I have seen occasionally all of the classical and so-called "pathognomonic signs" of ulcerative colitis, namely, shortening, narrowing and lack of haustrations (Fig. 60). This appearance is rarely permanent unless due to an actual inflammation of the colon. If due to irritability the same colon may show deep-cutting haustral contractions on the twenty-four- or forty-eight-hour mouth-meal films, indicating that the smooth appearance on the enema film is not the result of actual disease of the bowel wall.

**Treatment.**—The large group of patients with subjective complaints dependent upon colonic irritability constitute a real problem in office practice. Are the symptoms due to organic disease in the colon? An individual with a long history of irritable colon may, of course, develop an organic lesion. Ruling out this annoying possibility, isn't it remotely possible that there is a chronic pelvic inflammation, a mechanical appendix, a renal calculus or pyelitis? Mature judgment in the selection of diagnostic procedures and a period of observation is often essential before a definite decision can be made. What of the thyroid? Is the fatigue syndrome due to hypothyroidism? Does the extreme nervousness depend upon a not very obvious thyrotoxicosis? Does the menstrual irregularity depend upon a pituitary, ovarian or adrenal abnormality? Some cases will require complete surveys of this type before one can be sure. Was the previous dermatitis on an allergic basis and can one positively rule out food allergy? Possibly a detailed study of this kind may be necessary. How significant is the nervous factor? Why is the patient always symptom-free when away from home? Is the disturbing influence at home

or in business? Does an anxiety neurosis or hysteroid disposition play a part? Are the symptoms bona fide, or is the patient basically hypersensitive, or may the syndrome be entirely explained on a "substitution basis?" Should one institute a psychiatric study now or would it be wise to go slowly with this type of questioning for the present? Does tobacco play a part? Is bridge a factor, and so on ad infinitum? Here is an ailment in which equal attention must be paid to the psychic and the somatic sides. Here one needs the training of a well-rounded internist and psychiatrist combined with the sage wisdom of a philosopher. Those who approach this problem with a sense of security and smugness, using only stereotyped methods, are doomed to frequent failures. It is quite impossible to discuss the management of cases of this type in detail without writing a lengthy monograph. Briefly, the treatment may be considered under two headings: (1) measures directed toward the alleviation or cure of the underlying cause, and (2) local measures directed toward the colon.

1. *General Measures.*—Focusing primary attention on the colon is obviously treating only a symptom in most instances. The therapy of real value is that directed toward the cause of the vegetative nervous system abnormality if it can be ascertained. The psychic factor will need attention in many. This may mean a very definite readjustment based upon psychiatric study. Environmental changes may be necessary. Causes for outbursts of emotion, periods of depression and prolonged grief must be sought and alleviated in so far as possible. Removal to a hospital may temporarily ameliorate an imminent or immediate crisis and allow time for outlining a more deliberate and lasting plan. A holiday from home and business is frequently beneficial. Therapy must include avoidance of those factors which have been known to precipitate attacks. This may include public speaking, bridge playing, excessive smoking or overwork. Hygienic faults should be corrected if possible. Sufficient sleep, a mid-day rest, moderate exercise and diversion, and regular hours of eating in pleasant surroundings may prove beneficial. It is usually wise after explaining the nature of the illness to write out a specific program to be followed. Sedatives may be necessary to insure adequate sleep and al-



leviate mental anxiety. Specific measures may be indicated to correct an underlying abnormality of the endocrine system or an allergic state. Occasionally it seems advisable to remove surgically or treat medically a pathologic focus in some other abdominal organ, although, in my experience, chronic gall-bladder disease and so-called "chronic appendicitis" are rarely the cause of an irritable colon syndrome. If achlorhydria is present, dilute hydrochloric acid should be tried even in the absence of diarrhea, as it may improve the colonic instability. The healing of a duodenal ulcer will often bring about a cessation of colonic symptoms when the two conditions coexist.

2. *Local Measures.*—The diet should be bland during attacks and possibly free from coarse cellulose fiber at all times. Ice cold or very hot food and liquid are not advisable. The diet should be adequate in calories and balanced to contain all the essentials for normal nutrition. A carefully taken dietary history will often reveal inadequacies or indiscretions which can be corrected. Many of these patients become food faddists after long suffering and failure to obtain benefit from regular physicians and require intelligent handling to be convinced of the rationale of the diet prescribed. If the capacity of the colon is large and obstinate constipation is present, nonirritating residue in the form of agar, kaolin, or one of the mucilaginous preparations, such as Mucilose, Metamucil or Konsyl, should be used in sufficient quantity to insure the passage of stools of adequate size. Those who pass dry, fragmented stools should take mineral oil. The disagreeable leaking of the oil so commonly present in cases of spastic colon can be prevented by the addition of adequate quantities of one of the above substances. All irritating laxatives should be avoided. If constipation is marked, magnesium oxide may be used in sufficient quantities to overcome it in most instances. The dose can be gradually reduced as bowel function improves. One of the best drugs in these cases is belladonna. It may be prescribed as the extract with magnesium oxide and kaolin in powder form. One of the favorite prescriptions of the author is: Ext. bell. gr.  $\frac{1}{4}$ , calcined magnesia gr. 10, calcium lactate and kaolin 5̄ā dr.  $\frac{1}{2}$  three times daily before meals. Enemas and irrigations are not used except in emergency during the beginning of the regimen or during an attack in the manner

described below. We feel that the routine use of solutions injected into the bowel only tends to irritate the bowel and disturb its normal rhythm. For relief of pain which may be very severe during the acute exacerbation, principal reliance should be placed upon antispasmodics and sedatives. Atropine with bromides and phenobarbital is an excellent combination. Opiates should be avoided because of the chronicity of the condition and danger of habit. Better results will be obtained if the patient is confined to bed until the attack has entirely subsided. Hot, moist applications or a warm tub bath often help to alleviate the pain. A warm injection of several ounces of olive oil, cotton seed oil or a solution of barium sulfate may bring about rapid relief. A course of calcium and parathyroid seems of benefit in assisting to control a particularly severe attack in some patients. Dorst, Mateer, Berger and others have reported increased skin sensitivity to bowel organisms in some cases of irritable colon. Autogenous and stock vaccines of colon organisms have been found beneficial by these observers. Other methods of desensitization, such as the administration of sodium ricinoleate, 5 to 10 grains twice or three times daily, have been recommended by Dorst. The author has had little experience with vaccine therapy but has used sodium ricinoleate in those cases with allergic manifestations with some benefit. I doubt if this type of management strikes at the root of the trouble except in occasional cases and consequently do not recommend these measures routinely. The use of so-called "specific methods" of treatment for conditions which are probably not primarily bacterial does not seem rational.

**Case I. Illustrating Severe Colonospasm in a Patient with Obesity, Possibly of Pituitary Origin.**—M. P., a single female Jewess, twenty-seven years of age, appeared December 13, 1936, complaining of attacks of excruciating pain in the lower left abdominal quadrant of several days' duration, associated with frequency of urination and desire for frequent defecation. The attacks were of such intensity and frequency that the patient had spent a great part of her time in bed since the onset in November, 1935. She had been slightly constipated previous to the onset and often resorted

to mineral oil. Enemas, prescribed for the relief of pain, were discontinued because they accentuated the pain. Excessive fatigue and dizziness were subsidiary complaints.

The patient and her family were extremely apprehensive and nervous. She weighed 14½ pounds at birth and had been obese always. Menses started at the age of eleven years and occurred regularly thereafter, lasting six or seven days and accompanied by severe cramps. Since the onset of the present



Fig. 60 Case I Showing extreme narrowing and lack of haustrations. This can now be differentiated roentgenologically from chronic ulcerative colitis.

illness the lower left quadrant pain was always worse at the onset of menstruation.

The physical survey was negative except for masculine hair distribution, tachycardia and obesity; weight 170 pounds, height 60½ inches. The previous "best weight" was 240 pounds, four years previously. Weight loss resulted from a strenuous reducing diet, instituted in March, 1936, which seemed to aggravate the chief complaint. The blood pressure was 124 systolic and 78 diastolic. Examination of the feces,

urine and blood revealed nothing abnormal. The basal metabolic rate was minus 9. Venepuncture was refused so that sugar tolerance and blood cholesterol determinations have not been performed to date. The sigmoidoscope could not be passed beyond the rectum because of feces, spasm and apprehension. A small hemorrhoid was found. The pelvic colon was felt as a fountain-pen-sized tube which was exceedingly tender and this tenderness corresponded to the location of the chief complaint. Barium enema study failed to reveal diverticulosis or other organic colonic disease. The left colon maintained a narrow contracted lumen throughout the period of observation (chronic continuous colonospasm). Barium entered the colon at low pressure very rapidly and caused considerable discomfort. All semblance of normal haustral markings were absent. It would have been impossible to exclude advanced ulcerative colitis from the barium study alone (Fig. 60).

The patient was placed on a regimen including a bland, high vitamin, well-balanced diet, psychotherapy, small olive oil instillations into the rectum, heat to the abdomen, sedation, antispasmodics and calcium. Unfortunately she developed an acute hemorrhoidal crisis, requiring surgical treatment, which interrupted the irritable colon regimen. Since then she has improved somewhat. Endocrine therapy has been withheld up to the present.

The case is cited to illustrate the advanced state of ill health and suffering which may be anticipated in some cases. The extreme hypertonicity and narrowing of the left colon, noted in this case, is not infrequently associated with symptoms of great severity and frequency. The underlying vegetative instability is probably of pituitary origin conditioned by an anxiety state, the exact nature of which remains obscure.

**Case II. Illustrating the Irritable Colon Syndrome in Association with an Anxiety Neurosis, Achlorhydria and Abdominal Parietal Neuralgia for which Two Laparotomies were Performed without Relief.**—A. B., a married Italian female, was admitted to the Graduate Hospital, July 17, 1935, complaining of constant pain in the left midabdomen and alternating attacks of constipation and diarrhea with the

passage of mucus in the stools. There had been one pregnancy in 1930 which was followed by the first attack of diarrhea.

The past medical history is illuminating and will be given in some detail as it is typical of many patients of this type.

January, 1932.—Onset with postprandial, epigastric distress, nausea and vomiting. Treated for intestinal "flu"; no relief. Admitted to a hospital on the service of a gynecologist for two weeks. Released on diet and medication; no relief. Onset of diarrhea and midabdominal pain; sent to another physician. Diagnosis: *dropped stomach*. Admitted to second hospital for three weeks. Diagnosis: *intestinal tuberculosis*. Pain now centered about lower right quadrant. Colonic irrigations started. Admitted to third hospital; signed release.

May, 1932.—Admitted to fourth hospital. *Appendectomy* performed; no relief. Remained in hospital eight weeks on sedatives. Constipation severe. Suppositories started; weight dropped from 116 to 88 pounds. After one month admitted to fifth hospital. Some insight into true nature of affairs resulted in regimen for weight gain combined with psychotherapy. Weight rose to 135 pounds; returned to work February, 1933; remained quite well until:

November, 1934.—Nausea and vomiting recurred; mucus first appeared in stools; pain in left midabdomen recurred. A narcotic medicine was prescribed; no relief without it. Narcotics discontinued after four weeks. Readmitted to fifth hospital for study and intravenous medication for radiculitis.

February, 1935.—Admitted to sixth hospital. Disease of *left kidney* and *ulcerative colitis* was suspected. Oil enemas prescribed. Narcotics hypodermically were resorted to frequently. "Mucous diarrhea" and fainting spells.

March, 1935.—Admitted to seventh hospital. Tentative diagnosis of intestinal tuberculosis made. Signed release. "Daily needles."

April, 1935.—Readmitted to fifth hospital for midabdominal pain. Operation for release of *abdominal adhesions*; no relief. "Incision open and draining for 4 weeks." Home three weeks in bed with sedatives; no relief.

June, 1935.—Consulted another physician in another city who diagnosed *mucous colitis*. Suppositories prescribed.

On arrival at the Graduate (her eighth hospital), she

weighed 108 pounds; had been eating copiously of roughage and seemed to be in acute pain. The physical examination was negative except for slight hypertension (144/88) and tenderness in the abdominal wall just to the left of the umbilicus. The spine films showed very early arthritic changes in the lower thoracic vertebrae and slight dorsolumbar lordosis. The temperature and blood count were normal. Analysis of urine and feces showed nothing of consequence. Fractional



Fig. 61.—Case II. Film shows no evidence of colonic irritability although bowel function had been abnormal for five years. The fluoroscopic findings were typical of irritable colon.

gastric analysis revealed an achlorhydria. Histamine, however, elicited an acid response—HCl 15 after forty-five minutes. Sigmoidoscopy—normal mucosa of the rectum and sigmoid. The barium enema revealed a long colon, which was noted by the fluoroscopist to be extremely irritable and spastic, although the film (Fig. 61) does not indicate much spasticity. The capacity of the colon was not reduced but the introduction of the barium caused marked discomfort. The late Dr. Clarence Patten examined the patient and diagnosed

an anxiety neurosis probably dependent upon marital difficulties. Dr. William Bates injected novocain locally into the tender area of the parietes and brought about immediate relief of the tenderness.

Treatment consisted of postural corrective exercises, a bland diet, belladonna, phenobarbital, charcoal, bismuth and kaolin; sodium ricinoleate, rectal instillations of olive oil if constipated, hydrochloric acid after meals and psychotherapy with an attempt at improving domestic relations. She responded satisfactorily. She was seen in March, 1936, symptom-free and four months' pregnant.

The failure to appreciate the frequency with which parietal abdominal neuralgia and unstable colon may give rise to recurring bouts of severe abdominal pain accounts for this patient's round of visits to innumerable physicians and 8 different hospitals. The diagnoses included dropped stomach, intestinal tuberculosis, ulcerative colitis, appendicitis, abdominal adhesions and disease of the left kidney. The economic loss entailed by her illness is appalling. The opium habit was in the offing on two different occasions. It seemed likely that the anxiety neurosis may have been primary. The tendency to diarrhea was considerably increased by the achlorhydria, as she responded quickly to hydrochloric acid. However, the alternating constipation and diarrhea with excessive mucous discharge undoubtedly resulted from neuromuscular instability of the colon; the emotional factor being of paramount etiologic significance. The constant left abdominal pain was probably due to a localized parietal abdominal neuralgia, immediately the result of postural strain but conditioned undoubtedly by the underlying nervous hypersensitivity.

**Case III. Illustrating the Coexistence of an Irritable Colon (Prediverticulosis) and Duodenal Ulcer.**—A. D., a very nervous Italian tailor, forty-two years of age, was first seen in May, 1932, complaining of abdominal fulness and distention and diarrhea. The past medical history was not relevant. He was the father of 11 children. This may have accounted for his consumption of 40 cigarettes daily.

Stomach symptoms began in 1914, with generalized abdominal pains, worse in upper abdomen and referred to lower

weighed 108 pounds; had been eating copiously of roughage and seemed to be in acute pain. The physical examination was negative except for slight hypertension (144/88) and tenderness in the abdominal wall just to the left of the umbilicus. The spine films showed very early arthritic changes in the lower thoracic vertebrae and slight dorsolumbar lordosis. The temperature and blood count were normal. Analysis of urine and feces showed nothing of consequence. Fractional



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Stomach symptoms began in 1914, with generalized abdominal pains, worse in upper abdomen and referred to lower

dorsal spine on the left side. The pain was accompanied by distention and relieved by defecation. He likewise complained of late postprandial gnawing epigastric pain, relieved by eating or the taking of soda. These two syndromes had recurred at intervals every three or four months. The duration of attacks was from three to six weeks. A bout of diarrhea of five weeks' duration occurred in 1929 and a second attack lasting seven months occurred in 1930. Since then there have been

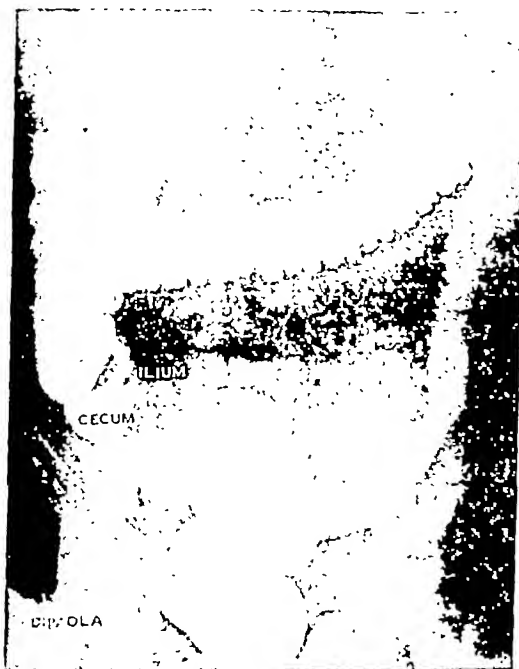


Fig. 62.—Case III. Extreme irritability of the left colon of the "prediverticulosis" variety.

frequent recurrences of several days' duration, usually after nervous upsets. The patient had never noted mucus, blood or pus in the stools. A diagnosis of duodenal ulcer, probably inactive, was based upon the roentgen demonstration of a markedly deformed duodenal cap and a moderate hyperacidity. Organic colonic disease was ruled out by fecal analysis, sigmoidoscopy and x-ray studies. The passage of the sigmoidoscope into the lower sigmoid was difficult because of spastic

contraction of the bowel. Inflation with air caused epigastric crampy pain quite similar to the upper abdominal pain of which the patient previously complained. This impression of bowel irritability was confirmed by barium enema. The capacity of the colon was one half that of normal. The lumen was narrowed and lacked normal haustral contractions. The whole left colon showed the fine saw-tooth markings which have been described by Spriggs and Marxer as prediverticu-



FIG 63.—Illustrating prediverticulosis in a female patient with long-standing irritable colon symptoms.

losis (Figs. 62, 63). Examination of the gallbladder, blood and urine revealed nothing noteworthy.

**Discussion.**—About 30 per cent of patients with irritable colon symptoms give a history of a duodenal ulcer syndrome (Bockus and Willard). These two symptom groups may occur simultaneously as they did in this patient or they may develop entirely independently of each other. The frequent concomitance of these two conditions may be advanced as an argument favoring an underlying neurogenic or vegetative ab-

normality common to both. In many patients with a colonic neurosis having in addition duodenal ulcer symptoms, the roentgenologic study of the upper tract will show only irritability of the duodenal cap but no ulcer niche. Quite a number of patients of this type subsequently develop a characteristic ulcer defect. This observation likewise lends support to the importance of the neurogenic factor in ulcer pathogenesis.

Further evidence supporting the neurogenic background in our patient was the history of the development of rapid blanching and coldness of the skin of both hands when the arms were elevated. No detailed studies of the peripheral vessels were carried out but there was nothing to suggest organic peripheral vascular disease.

This case illustrates the diagnostic importance of the sigmoidoscopic examination. Spasm and abdominal pain simulating the chief complaint were induced by the introduction of the instrument and inflation with air. Symptoms of great severity have been noted in many patients showing the roentgen signs of so-called "prediverticulosis." This type of bowel silhouette is almost always associated with irritable colon symptoms in my experience.

## CLINIC OF DR. LOUIS TUFT

### TEMPLE UNIVERSITY HOSPITAL

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#### ASTHMA AND HAY FEVER: THEIR ETIOLOGIC RELATIONSHIP AND CLINICAL IMPORTANCE

THE association of bronchial or allergic asthma with seasonal hay fever is a fairly frequent and generally recognized occurrence. The exact etiologic relationship existing between these two conditions as well as its clinical importance has not always seemed as clear nor has it been sufficiently emphasized. A critical analysis of this aspect of the subject seems worthy of presentation.

Asthma and hay fever may be present in the same patient and bear one of several different relationships. Thus, asthma of an allergic and perennial type may occur in a patient with seasonal hay fever and yet be independent of the latter. The asthma in such instances may be provoked by sensitivity to a food or to an inhalant allergen like dust, feathers, etc., whereas the hay fever symptoms are brought on by contact with plant pollen. The association here is one of coincidence and not one of cause and effect. Such a type is illustrated in the following case report:

**Case I.**—Male, age forty-six, first seen in outpatient allergy clinic in November, 1935, because of asthma, hay fever and eczema. The latter condition (eczema) first began on the face in early childhood and gradually spread to the other parts of the body involving particularly the flexures. It has persisted to present time. Condition is worse in the winter time. In 1930, began having recurring bronchial "colds" consisting mostly of coughing attacks. Since 1932 has had recurrent attacks of asthma worse in the early morning hours. Both the skin condition and the asthma are aggravated by dog contact. In 1932 also developed seasonal attacks of late spring and fall

hay fever of a mild type. These have recurred each year and are not accompanied by asthma or exacerbation of the eczema.

Skin tests revealed definite positive reactions to ragweed, timothy and plantain pollens, important in the etiology of the hay fever and to dust, feathers, dog epithelium, and a number of foods, important in the asthmatic and cutaneous conditions. Patient is at present under allergic treatment and has shown considerable improvement. This is particularly evident in the hay fever symptoms, which have almost completely disappeared. The asthma and eczema still show a tendency to recurrence or aggravation especially after dietary indiscretion and dust or dog contact.

This case report illustrates an instance of perennial asthma and seasonal hay fever occurring in a highly allergic individual and yet bearing no etiologic relationship to one another. As a matter of fact, the connection between the asthma and eczema is much closer since both these conditions are made worse by the same allergens. The hay fever symptoms are really so mild as to be almost completely overshadowed by the other allergic conditions and are responding better to treatment.

The type of asthma present in the latter patient occurs throughout the year and has no seasonal incidence. It is known, therefore, as *perennial asthma* in contrast to those types which are either limited to a certain season of the year or at least begin during the same season of the year, and are therefore referred to as *seasonal asthmas*. Since sensitivity to pollens usually is responsible for the latter type, it is often known as *pollen asthma*.

Seasonal asthma may appear in one of three different forms: (1) it may be the only manifestation which the patient presents or at least the major symptom; (2) it may occur as a complication of a seasonal hay fever, the asthma appearing some time after the onset of the hay fever symptoms and disappearing at the conclusion of the pollinating season; or (3) it may begin as a complication of hay fever but become prolonged for weeks or months after the completion of the pollination period and after the nasal and ocular symptoms of hay fever have disappeared. This type may eventually become perennial.

The occurrence of seasonal asthma without any nasal or ocular manifestations of hay fever is extremely uncommon. Its characteristics, as well as the diagnosis and treatment are similar in every respect to the ordinary uncomplicated seasonal hay fever. The only manner in which these conditions differ is that in the hay fever patient the shock tissue containing the sensitive cells is located in the nasal and ocular mucous membranes, whereas in the individual with pure seasonal asthma, it is located in the lining mucosa of the bronchial tubes. This is exemplified in the following case report:

**Case II.**—Male, age fifty-eight, first seen in September, 1931, with a history of seasonal asthma of twenty-seven years' duration. Attacks begin with dyspnea and wheezing followed later by cough and expectoration. They are particularly bad in the early morning hours between 1 and 7 A. M. and are relieved only by a hypodermic of adrenalin. Attacks come on daily from June 15th until the early part of September when they disappear suddenly and completely. Patient is free of symptoms throughout the rest of the year. *Sneezing, rhinorrhea, or itching of the eyes have never occurred* during these attacks.

Skin tests revealed sensitivity to timothy, plantain and corn pollens. Treatment with a mixture of the extracts of these pollens was advised in consequence.

The important feature in the latter patient is the occurrence of a strictly seasonal asthma in the complete absence of any of the usual symptoms of hay fever. As mentioned previously, this type is very unusual. As a rule when the asthma is seasonal and begins with the onset of the hay fever season, the ordinary nasal and ocular symptoms of hay fever occur at the same time but the asthmatic symptoms are much more prominent than those involving the nose or eyes. This is explained immunologically upon the basis that the shock organ in these patients is located not only in the nasal and ocular mucosae but in the bronchial mucous membrane as well and the cells of both areas are highly enough sensitized to react to contact with the pollen antigen in the form of symptoms of both asthma and hay fever. Consequently, therefore, the

asthmatic symptoms begin at the onset of the hay fever season and at the same time as the nasal and ocular manifestations.

Although the coincident equivalent sensitization of both shock tissues (*i. e.*, upper and lower respiratory) giving rise to asthma and hay fever symptoms at the very onset of the season is possible, it is not the common type by any means. Detailed inquiry into the histories of many of these patients reveals the fact that when the condition first begins, the upper respiratory manifestations exist either alone or are predominant and that the asthmatic symptoms begin some time after the onset of the hay fever. In other words, since the pollen allergen comes in contact with the nasal tissues first, these are the first to react and hay fever symptoms are produced. When the concentration of pollen becomes very marked, the bronchial shock organ of certain patients may then react and asthma results.

The presence or absence of asthmatic symptoms in hay fever patients is dependent, therefore, upon the reactivity of the bronchial shock organ and the concentration of pollen in the atmosphere. If the bronchial tissues are highly reactive, asthma may come on early in the season from ordinary pollen concentrations. If it is not as reactive, asthmatic symptoms may not become evident until the height of the season when pollen concentration reaches its maximum. As a matter of fact, clinical experience has indicated that the onset of asthma at some time during the pollinating season and after the onset of the ordinary hay fever symptoms is the most common manner in which these two conditions are associated. Most of these patients give a history of having had hay fever for some period of time, possibly for years prior to the onset of the asthmatic condition. The symptoms are those of sneezing, watery rhinorrhea, nasal obstruction, itching of the eyes and lacrimation. There is no cough, dyspnea or wheezing. This recurs season after season without any change, the symptoms disappearing completely and often suddenly at the end of the pollinating season. After several seasons and especially at the time at which the pollen concentration of the atmosphere is highest (about ten days to two weeks after the onset), the patient begins to show signs of tracheal or bronchial involvement in the form of an irritating unproductive cough.



This responds fairly well to the ordinary remedies and even if untreated, it diminishes or disappears when the pollen concentration lessens so that it is gone completely along with the other symptoms by the end of the season. This may continue for one, two or more seasons and then the patient will notice that in addition to the cough there is present a constriction or heaviness in the chest, possibly some dyspnea or even a slight wheeze, present especially or only at night. These symptoms likewise disappear at the end of the pollinating season and are neither constant nor pronounced. This syndrome of hay fever symptoms only, followed by the appearance of the irritating cough and in subsequent seasons by definite dyspnea and wheezing, is one which can be obtained by detailed inquiry into the histories of patients with seasonal hay fever and asthma, as for example in the following case report:

**Case III.**—Male, age twenty-nine, first seen May, 1934, because of seasonal hay fever and asthma. The hay fever at first was of the late or autumnal type, coming on about the middle of August and persisting until the first frost. It first began in 1929 and for the first two seasons was accompanied only by the usual nasal and ocular manifestations. In 1931 and again in 1932 patient noticed that two weeks after the onset of the hay fever symptoms, an irritating unproductive type of cough appeared. This lasted until the end of the season and disappeared along with the other manifestations. In 1933 the hay fever symptoms were quite severe and were followed in the early part of September by severe cough, pain in the chest, and dyspnea of a definite asthmatic type. These symptoms were so marked that the patient had to remain in bed for nearly four weeks because of the danger of bronchopneumonia. All symptoms disappeared at the end of the pollinating season. In 1932 patient developed the usual symptoms of early hay fever lasting from the first week in May to the middle or end of June and recurring in 1933. Cough was present in the middle of the season but there was no wheezing associated with it. Except for an occasional winter cold, patient is quite well during the free interval. Hay fever symptoms are markedly aggravated by dust contact during the season, although patient has no symptoms from this contact

at other times of the year. He also notices that the ingestion of such citrous fruits as orange, grapefruit, or lemon during the hay fever season causes itching of the palate or sneezing but not at other times of the year. Except for a history of late hay fever in two maternal uncles, the balance of the history is unimportant.

Skin tests by the intracutaneous method to the important allergens revealed the following:

Marked reactions to: ragweed, birch and walnut tree pollens, and wheat.

Moderate reaction to: house dust and silk.

Slight reaction to: timothy and plantain pollens, orange, cheese and garlic.

Doubtful reaction to: potato, spinach, and crab.

Pollen desensitization with timothy, birch tree and ragweed extracts was begun immediately and continued throughout 1935 and 1936. Marked improvement of early hay fever occurred throughout each year. In 1934, patient obtained more than 75 per cent relief of the late hay fever symptoms and although asthma was absent, slight cough was present for several days at the height of the season. Almost complete relief occurred in 1935 and 1936 and neither cough nor wheezing was present.

This case demonstrates very nicely the commonest type of association between asthma and hay fever. It is important to note that the irritating cough in this patient was present for two seasons prior to the onset of the dyspnea and wheezing. *The appearance of an irritating cough at the height of the season in a patient with the usual symptoms of hay fever should be considered a danger signal warning of a possible asthmatic complication.* Since it has been estimated by various authors that more than 50 per cent of all hay fever patients who do not take treatment eventually develop asthma either of a seasonal or perennial character the importance of the above statement from a prophylactic standpoint becomes obvious. In most of these patients, the hay fever and the associated or complicating asthma are due to sensitivity to the same pollen. The asthma comes on only when the pollen concentration reaches its height or when it is greater than the

nasal shock organ can withstand. The nasal tissues in the hay fever patient as in the normal act as a defender against pollen invasion and it is only when the latter is overpowering in amount that the defense is broken down and the bronchi are involved. This is just as true in this type of case as in a constitutional reaction from a pollen injection, in which asthma may occur as part of the general reaction in a patient with ordinary hay fever who never previously had any asthmatic symptoms. That the pollen sensitivity is likewise responsible for the asthmatic complication is indicated by the fact that as the pollen concentration in the atmosphere lessens, the asthma diminishes and when the pollinating season is terminated, all evidence of bronchial irritation disappears in most patients. It is obvious that the milder the symptoms are in these patients the less tendency there will be for the occurrence of bronchial symptoms. It is for this reason that symptoms of bronchial irritation are the first to disappear in patients receiving pollen therapy. Treatment may not always render the patient completely free of his hay fever symptoms but it will rid him at once of the asthma produced by pollen sensitivity. This was illustrated in Case III as well as in the following patient:

**Case IV.**—Male, age twenty-five, first seen in May, 1934, with a history of late hay fever present since 1922. Symptoms were of the usual nasal and ocular type at first, but for the past few years has had coughing and wheezing spells at the height and toward the end of the season. Treated previously by pollen desensitization with little or no relief. Except for occasional attack of rhinitis in winter, general health is good. Family history reveals migraine in mother, late hay fever in brother and asthma in paternal grandfather.

Skin tests to pollens showed marked sensitivity to ragweed pollen. Pollen desensitization with ragweed extract was begun in May, 1934, and continued throughout the hay fever season and upon an annual basis since. In 1934, patient obtained from 50 to 75 per cent relief of symptoms and though he had no asthma, the cough was present for several days during the height of the season. However, in 1935 and 1936 when

the amount of relief was even greater, neither the cough nor the asthma was present.

*The ability of pollen desensitization to prevent the onset of the asthmatic complication is probably its most outstanding virtue.* Practitioners would do well to emphasize the necessity for pollen therapy for this reason alone rather than for the relief of the hay fever symptoms per se.

For the successful eradication of the asthma in these patients, proper and adequate treatment is essential. Improper treatment obviously will fail in its accomplishment and serve to prolong rather than relieve the condition. By the same token, anything which serves to interfere with the proper treatment, as for example the existence of complicating infections or the presence of additional sensitivities will tend to prevent a successful response to pollen therapy. These extra-pollen factors are more likely to occur in those patients with seasonal hay fever and asthma of long standing who have not had any treatment, or in whom treatment has not been adequate—thus patients may develop symptoms from exposure to dust or feathers or foods or other allergens during the pollinating season and not be affected by them at other times of the year. It is essential, therefore, that patients with seasonal asthma and hay fever who are insufficiently relieved by pollen therapy should be thoroughly investigated to determine the possible presence of factors other than the pollen. This is exemplified in the following case:

**Case V.**—Male, age twenty-one, first seen in March, 1934, because of seasonal hay fever complicated by asthma. Hay fever symptoms first began in August, 1925, and have recurred every year since, lasting until the end of September or the first week in October. Mild nocturnal asthma usually accompanies nasal and ocular symptoms of hay fever toward the end of the season. In June, 1932, developed mild hay fever symptoms of the early summer type, lasting only a short time. Subject to attacks of urticaria attributed to ingestion of tomato.

Skin tests showed definite sensitivity to many allergens—the most important, however, were ragweed, timothy and plantain pollens.

Pollen desensitization with timothy and ragweed extracts was begun in the spring of 1934 and continued throughout the fall. Although the dosage, particularly of the ragweed pollen extract, was increased to a very high point, the patient had no relief of his hay fever symptoms at all and very little relief of the asthma. The injections were continued upon a perennial basis throughout 1935 with little additional relief. Upon closer inquiry it was found that the patient had failed to eliminate those allergens from his diet or environment to which he was sensitive. This was carried out during the 1936 season and in addition injections of dust extract were given. The pollen extract, however, had been maintained at the same level throughout. Under this régime there was marked improvement in 1936 over any previous season, the patient experiencing more than 75 per cent relief and having no asthma.

The latter patient illustrates exceedingly well the manner in which extra-pollen sensitivities may prevent a successful outcome since the pollen dosage during the two years in which no benefit occurred was exactly the same as that during the year when the extra-pollen factors were being taken care of. It also emphasizes the importance of a complete allergic study in those patients who fail to respond to pollen therapy.

These extra-pollen factors seldom aggravate the pure or uncomplicated type of seasonal asthma. They are more likely to influence that type which is associated with hay fever symptoms. Their most common effect in these patients is to produce a prolongation of the asthma beyond the pollinating season. In such instances, the patient usually gives a history of hay fever symptoms only for several seasons, then the hay fever is complicated by asthma which comes on at the middle of the season and terminates at the end. This continues for several seasons when it is noticed that the asthma instead of disappearing at the end of the season is prolonged for variable periods of time beyond the usual limit. These prolongations become greater and greater as the years go by. Since pollen is absent from the atmosphere after the season is over, it is evident that the asthma could not be due to pollen contact, although the latter was responsible for initiating it. Factors other than the pollen obviously must be at fault. These fac-

tors may exist in the form of sensitivity to inhalant, food or bacterial allergens or to infection of the paranasal sinuses or even to such physical factors as heat or cold sensitiveness as suggested by Duke. The following case report is an example of this type:

**Case VI.**—Female, age thirty-one, first seen in December, 1932, because of recurrent attacks of asthma complicating a fall type of hay fever. The latter first began in 1917 following a visit to the country and was accompanied at first by the usual nasal and ocular manifestations beginning about the middle of August and lasting until the end of September. In the last few years, patient has developed asthma which comes on at the height of the season. This disappears usually at the end of the season, but in 1930 and 1931 it has shown a tendency for prolongation into October and during 1932 the asthma persisted in nocturnal form until December. Attacks are aggravated at the seashore or after exertion and are lessened at higher altitudes. For the past three years, patient has had symptoms of early hay fever coming on in May, complicated in June by mild asthma but disappearing usually in July. During the rest of the year, patient is subject to attacks of rhinitis of a bacterial type. Frequent colds as a child. Because of this, patient had two tonsil operations in 1911 and 1916; also, a submucous resection in 1923 and an operation on the ethmoids in 1928. History of asthma in a paternal cousin.

Nose and throat examination, including x-ray of the sinuses, showed the presence of bilateral ethmoidal infection with beginning atrophic changes and also hyperplastic changes of the *left maxillary and frontal sinuses*.

Skin tests by the intracutaneous method showed the following:

Marked reactions to: house dust and ragweed pollen.

Moderate reactions to: timothy and plantain pollens.

Slight reactions to: feathers, goat epithelium, spinach and celery.

Doubtful reactions to: wheat, chicken and flounder.

Allergic studies were carried out in December, 1932, and treatment instituted in January, 1933. By this time, asthmatic attacks had disappeared and patient remained free until May,

1933, when symptoms of hay fever and asthma recurred in spite of dust and pollen desensitization and local nose and throat treatment. Patient was symptom-free in July but symptoms recurred in August and continued in spite of treatment until January 1, 1934, when they disappeared. The same program was repeated in 1934 with the addition of autogenous vaccine administration. Symptoms recurred in May and June and again early in August. On August 15, patient went to the mountains near Kane, Pa., and later to Toronto, Canada. Although symptoms were rather marked in both these places, they were not so severe as at home. The asthmatic attacks continued until October 15 when they disappeared suddenly and completely and did not return again even upon the patient's return to her own residence several weeks later.

In the latter patient, the presence of the sinus infection as well as the sensitivity to other allergens and the effect of climatic changes served to prolong the asthmatic symptoms beyond the hay fever season until late in December. That these factors were of importance is evident from the fact that change of residence was followed by some relief of symptoms and disappearance of the asthma on October 15th.

It is important to recognize this type of patient and to institute treatment early because it is in such a patient as this one that perennial asthma, severe enough to overshadow completely the seasonal manifestations, is likely to develop. Sometimes the transition to perennial asthma is gradual—the patient has the ordinary hay fever symptoms at first; this is complicated after several seasons by asthma which is at first of the strictly seasonal type but later tends to become prolonged beyond the season as the result of extra-pollen factors. If this continues, the asthmatic attacks are not only prolonged beyond the hay fever season but begin to occur throughout the year, so that the patient not only has seasonal asthma but one which is perennial as well. Either of these types may then predominate, although aggravation of the asthma during the hay fever season as well as nasal manifestations usually are evident in most patients. In a few, however, the transition to the perennial type of asthma occurs rather quickly and after only a short period of seasonal symptoms. This type is rather

dangerous because the asthma is likely to terminate as a severe chronic intractable type, as for example in the following case report:

**Case VII.**—Female, age sixty-four, first seen in clinic in December, 1932, with a history of asthma since 1907. At first the asthmatic attacks accompanied the ordinary symptoms of seasonal hay fever of the fall type, beginning in August and lasting six weeks. In 1910, the seasonal incidence extended from June to September and the asthmatic attacks began to assume a perennial character. They became increasingly severe in character so that the patient had to discontinue her occupation as a weaver and have been almost continuous since. Condition is aggravated by exertion and exposure to dust and not improved by change of climate. Patient had migraine at the age of twenty, which lasted several years and subsided spontaneously.

Except for a history of asthma in a maternal aunt, the history is unimportant.

Examination shows marked emphysema with asthmatic râles throughout the chest. Blood pressure 150/90. Heart on x-ray examination showed definite enlargement; the lungs showed changes at the bases attributable either to passive congestion or old inflammatory disease with scarring and pleural thickening and the possibility of bronchiectasis to be considered.

Skin tests by the intracutaneous method showed:

Marked reactions to: house dust, feathers, chocolate.

Moderate reactions to: black pepper.

Slight reactions to: barley, tea, beech tree and timothy pollen.

Doubtful reactions to: wheat, cornmeal, orange, rice, green pea, spinach, peanut, oats, coffee and ragweed pollen.

Patient was placed on appropriate therapy including dust and pollen desensitization for a period of a year but without any change in her asthmatic conditions, the attacks being almost continuous. Patient, therefore, discontinued her visits to the clinic.

A significant feature of the latter case report is the fact that the asthma at first was of the seasonal type and accom-



panied the ordinary symptoms of hay fever. It then became perennial and overshadowed completely the seasonal symptoms. When seen at the clinic the patient was a chronic intractable asthmatic with definite and marked tissue changes and a hopeless prognosis. If treatment could have been instituted when the symptoms were limited to the hay fever season, it is very likely, in view of the favorable response of pollen asthmatics to therapy (as illustrated by Cases III, IV and V), that she would have been spared the untold misery and suffering which ensued in subsequent years. This case emphasizes, more than any of the preceding ones, the necessity for instituting pollen therapy early in hay fever patients as a prophylactic measure against a complicating asthma which may be of a severe or intractable type.

#### SUMMARY

Asthma appearing in patients who have seasonal hay fever may occur either independently of the latter and have no etiologic connection, when it is known as *perennial asthma*, or, as is more common, it may occur as a seasonal manifestation and have a definite etiologic relationship. The latter form is referred to often as *seasonal* or *pollen asthma*, since it occurs in pollen-sensitive individuals. Seasonal asthma may appear in one of three ways: (1) it may appear as the only manifestation of pollen allergy, (2) as an accompanying manifestation of seasonal hay fever, or (3) as a complication of hay fever.

The first type, constituting a true pollen asthma, is one in which the patient has asthmatic attacks recurring regularly each season in the same way as in hay fever and subject to the same variations but not accompanied by nasal or ocular symptoms. In other words, the site of the affection or shock tissue involves only the bronchial mucous membrane.

In the other two types, the patient has the ordinary symptoms of hay fever but in the middle or toward the end of the season develops asthma of a mild or severe character. The onset of these symptoms may be indicated frequently by the presence of cough or constriction in the chest without definite asthma. These symptoms recur each year with increasing intensity until definite asthmatic attacks begin.

In patients belonging to the second group, the asthma is due entirely to the effect of the large amount of pollen acting not only on the nasal shock tissue but upon the bronchial mucosa as well. The asthma in these patients usually disappears rather suddenly with the cessation of the hay fever symptoms at the end of the season.

In patients comprising the third group, the asthma is the result of either specific or nonspecific factors other than the pollen itself; thus, such physical agents as a cold wind or the inhalation of such allergens as dust, feathers, orris root, etc., or the ingestion of certain allergenic foods, or the presence of infection of the sinuses may serve to provoke asthma in these individuals. Such extra-pollen factors may cause asthma during the hay fever season or prevent a satisfactory response to treatment, even though they have little or no effect upon the patient at other times of the year. They most frequently act to prolong the asthmatic symptoms beyond the hay fever season and for variable lengths of time after the nasal symptoms have disappeared.

These patients are especially prone to develop a perennial type of asthma which may completely overshadow the seasonal manifestations or may in some patients develop into the severe chronic intractable type of asthma so resistant to treatment. Since asthma is the first symptom to disappear in properly treated cases, the importance of early diagnosis and of the institution of proper and adequate treatment in patients with hay fever, either alone or accompanied by asthma, becomes obvious from a prophylactic standpoint.

## CLINIC OF DR. DAVID L. FARLEY

### PENNSYLVANIA HOSPITAL

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#### ACUTE INFECTIOUS MONONUCLEOSIS

THE name "Drüsenfieber," glandular fever, was given by Pfeiffer<sup>12</sup> in 1889 in his first description of the disease which we now call "infectious mononucleosis." Pfeiffer no doubt gave the disease this name because, as is well known, the lymph nodes are affected. It seems better, since lymph nodes are not properly referred to as "glands," to use the term "infectious mononucleosis." Even this term is slightly misleading because of its implication that the abnormal cells found in the blood picture of this condition are always "monocytes."

The etiology of infectious mononucleosis is unknown. The pathogenesis is obscure. Opinion varies between two points of view as to the mode of production of the blood picture peculiar to this disease; that it results from the characteristics of the organism specifically producing the disease; or that it is a picture which may result from tissue reaction in response to more than one etiologic agent.

Until recently the histologic features of the involved lymph nodes were not well known because of the paucity of biopsic and necropsic material. An article by Downey and Stasney<sup>7</sup> goes very fully into the pathologic histology. In a series of biopsied lymph nodes of 8 cases of infectious mononucleosis various stages in the lymph node histology were studied. There was a hyperplasia of reticulum involving both the sinus reticulum and the general reticulum. The hyperplasia of small lymphocytes in some of the nodes was suggestive of early lymphatic leukemia with the important exception that the architecture of the nodes never showed complete obliteration as is seen in lymphatic leukemia, and the capsule of the lymph nodes was not invaded. It appeared that the peculiar atypical cells which were seen in smears from the peripheral blood originated in the lymph nodes, since so many of these atypical

and leukocytoid lymphocytes were seen in the lymph node sections.

The point of view that the so-called "abnormal cells" found in the blood smears are lymphocytes rather than monocytes is borne out by the studies of Stuart, Burgess, Lawson and Wellman<sup>13</sup> who concluded from the use of the supravital staining technic of Wilson and Cunningham<sup>17</sup> that the abnormal cells are lymphocytes. They<sup>13</sup> believe that in this disease a strong stimulus to cell division in the germinal centers in the lymph nodes and spleen results in the peculiar appearance of the lymphocytes in the circulating blood.

Infectious mononucleosis becomes of importance to the practicing physician because of the resemblance of the blood picture at times to that of the more serious and uniformly fatal disease, leukemia. This resemblance leads to great alarm over the prognosis in the particular patient until it is found that the condition is really the relatively benign disease, infectious mononucleosis. The brilliant work of Paul and Bunnell<sup>11</sup> who showed that the so-called "heterophile antibodies" are greatly increased in infectious mononucleosis, together with the observations of Downey and Stasney<sup>7</sup> and Stuart, Burgess, Lawson and Wellman,<sup>13</sup> has stimulated the interest of the immunologist in this disease. There seems little doubt that serum from individuals suffering from infectious mononucleosis will agglutinate sheep cells in much higher dilution than serum from patients suffering from other infectious diseases—with the possible exception of serum sickness. The observations of Paul and Bunnell<sup>11</sup> have been verified by Bernstein,<sup>3</sup> Davidsohn,<sup>5</sup> and others. There is, however, some question as to whether the heterophile nature of the antibody in infectious mononucleosis can be unreservedly accepted.<sup>13</sup>

The details of 12 cases of infectious mononucleosis follow:

**Case I.**—C. R. T., age twenty-eight, admitted August 8, 1933, discharged August 29, 1933.

The patient was a young physician, a hospital resident. The onset of his illness was after a strenuous tennis game. He was affected with a sore throat, fever, and malaise. He had a constant fever for six days and for several days thereafter his fever continued with a slight rise to 99° F. in the afternoon. His pulse was never higher than 110 per minute. The

physical examination of the patient showed the throat to be diffusely reddened and edematous with much lymphoid hyperplasia of the pharynx. A definite gingivitis was present. The gums bled easily. Small ulcers developed in the mouth on each side of the posterior part of the hard palate. Smears from the lesions of the mouth, throat, and gums showed Vincent's bacilli and chains of streptococci, green streptococci predominating. Sodium perborate and gentian violet were used for the mouth lesions. Ulcers also developed on the tip of the tongue and several petechiae developed on the mucosa covering the hard palate. All the mouth lesions were very painful. In the neck the anterior lymph nodes were enlarged and tender. There was no enlargement of the postcervical nodes but a slight enlargement of the nodes in axillae and groins was evident. The enlarged lymph nodes persisted during the fever period. The spleen was enlarged and easily palpable. This enlargement persisted throughout the period of fever. The urine analyses showed nothing abnormal. The blood sugar, August 16, 1933, taken in the morning after fasting, showed 84 mg. per cent.

The blood counts were as follows:

Date.	Hb.	R. B. C.	W. B. C.	Poly.	Eo.	Bas.	Lymph.
8/8/33	92	4700	7,150	28	2	..	70
8/8/33			10,400	35	..	..	65
8/8/33			9,900	37	..	..	63
8/10/33			14,000	34	..	..	small 26 66 large 40
8/11/33			8,500	30	..	..	small 19 70 large 51
8/12/33			9,900	48	..	..	small 28 52 path. 24
8/13/33			9,500	39	..	..	small 30 61 large 31
8/14/33			9,300	38	..	..	small 28 62 path. 34
8/15/33			8,000	56	..	..	small 32 44 path. 12

The following notation was made on the second count dated 8/8/33. Smears showed normal R. B. C. The 65 per cent lymphocyte count included all the monocytes. At least half of these cells were large cells with irregular nuclei and deep-staining chromatin. Many were vacuolated. They appeared to be of lymphocytic origin and typical of the cells seen in infectious mononucleosis.

**Case II.**—C. E. S., age twenty-six, admitted April 4, 1929, discharged April 13, 1929.

The patient was a young physician, at the time a hospital resident. For six days the patient had a prodromal period of chilliness and malaise, then the onset occurred with a shaking chill on April 3, 1929. At this time the temperature was 101° F. The patient's fever varied from 99° to 100.5° F. over a period of six days and then became normal. Physical examination showed the posterior cervical lymph nodes to be slightly enlarged, and an increased area of splenic dulness to percussion was noted. The axillary and epitrochlear nodes were not palpable.

The blood counts were as follows:

Date.	Hb.	R. B. C.	W. B. C.	Poly.	Eo.	Bas.	Lymph.	M n.
4/ 7/29	10.9	4280	....	f. 23 28 nf. 5	..	..	64	8
5/15/29	..	....	8000	f. 63 76 nf. 13	.	1	19	4
8/ 1/29	9.3	4590	7300	72		..	25	3

**Case III.**—P. M. B., age twenty-two, admitted May 14, 1935, discharged May 20, 1935.

The onset occurred four days after a tooth extraction. At this time there was a feeling of a lump in the throat when swallowing. The patient continued his usual activities until he was told that he had a tonsillitis. At this time, May 14, 1929, he had a tender sore throat and "lumps" in his neck. His throat was found to be congested, there was a bilateral moderate cervical lymphadenopathy. His spleen was distinctly palpable. For four days the patient's temperature varied from

99° to 100° F., and then became normal. The urine analyses were negative.

The blood counts were as follows:

Date.	Hb.	W. B. C.	Poly.	Eo.	Bas.	Lymph.	Mon.
5/15/35	..	9,400	f. 10 26 nf. 16	3	..	52	19
5/13/35	..	12,500	f. 26 36 nf. 10	..	..	34 lymph. 40 path.	

**Case IV.**—H. S. F., age 19, admitted January 10, 1930, discharged January 19, 1930.

The patient was a worker in the post office. The onset of his illness occurred after physical exhaustion from prolonged hours of Christmas holiday mail rush. He was affected with chills and malaise; his throat felt irritated and dry but not definitely sore. There was no coryza or nasal discharge. For about two weeks his temperature varied from normal to 104° F. The physical examination of the patient showed a marked bilateral posterior cervical lymphadenopathy. The mucosa of the pharynx and the posterior part of the mouth were injected but showed no other evidence of soreness. The spleen and liver were not palpable. The urine analyses were negative. x-Ray of the sinuses was negative.

The blood counts were as follows:

Date.	Hb.	R. B. C.	W. B. C.	Poly.	Eo.	Bas.	Lymph.	Mon.
1/10/30	90	4700	25,000	16	..	..	26	58
1 14 30	.	....	11,000	40	..	..	32	28

**Case V.**—E. C. A., age twenty-five, admitted January 7, 1924, discharged February 4, 1924.

For a month before the onset the patient felt "run down," tired easily and felt exhausted. At the time of the onset there was tenderness in the back of the neck. At this time he had a fever and headache and slight epistaxis on blowing his nose. His temperature was rather prolonged, recorded from January 7 to January 22 (three weeks), and varied from 99.2° to

102.3° F. Physical examination showed a slightly congested pharynx. The lateral and posterior cervical lymph nodes were distinctly enlarged, discrete, hard and tender. The lymph nodes in the axillae and inguinal regions were greatly enlarged, discrete and tender. The epitrochlear nodes were readily palpable. The nodes varied in size from 0.5 to 1.5 cm. in diameter. There was expectoration of small amounts of blood, probably from the nasopharynx. The liver was enlarged, being 7 cm. below the costal margin in the right midsternal line. Jaundice was marked. The spleen was enlarged. There were no skin eruptions. The patient was irrational at times. Ten days after the onset the lymph nodes became smaller. An oxydase stain of the predominating large cells in the blood smears showed an absence of granules, in the cell cytoplasm of the abnormal cells. The spleen remained palpable for at least three weeks after the onset. The urine showed at various times bile and a heavy cloud of albumin.

The blood counts were as follows:

Date.	Hb.	R. B. C.	W. B. C.	Poly.	Lymph.	Mon.	Eo.	Bas.	Path.
1/19/24	85	5540	11,000						
1/11/24	..	.	.	23	7	2		2	70
1/13/24	.		16,400	13	12		2	3	60
1/15/24	90	5470	10,500	coagulation time 5 minutes.					
1/17/24	.	.	18,800	31	6	1			62
1/23/24	85	4340	9,400	12			2		85
1/28/24	85	4920	6,700						
2/ 3/24	80	4600	5,600	22					78
12/17/29	98	6140	7,800	37 5	52	7 5	2 5		0 5
7/16/34	87	4740	5,600	54	13 5	2	0 5		

This patient was followed through the courtesy of Dr. John B. Barnwell. The blood counts of 12/17/29 and 7/16/34 were made by Dr. Raphael Isaacs who noted that "immature lymphoid cells were present. On both occasions, but more marked on the examination of 12/17/29, cells of the infectious mononucleosis type were present."



**Case VI.**—W. H. L., age twenty-five, admitted June 28, 1925, discharged July 27, 1925.

At the onset of his illness the patient had chills, headache and malaise with enlarged inguinal nodes on the right side. He was found later to have a chancre which produced a positive Wassermann reaction of the blood. He began to run a slight fever and developed a sore throat. The temperature varied from 99° to 104.4° F. for seventeen days. Physical examination showed a congested sore throat, with no definite lesions. The lymph nodes in the postcervical and anterior cervical chains were slightly enlarged. There was a slight generalized enlargement of the lymph nodes. The spleen was questionably palpable. The liver was not enlarged and there was no jaundice. Urine analyses showed a cloud of albumin on two occasions, but no casts.

The blood counts were as follows:

Date.	Hb.	W. B. C.	R. B. C.	Poly.	Lymph.	Eo.	Ab. Mon.	My.	Bas.
6/29/25	100	14,400	5200						
7/ 5/25	.	13,250							
7/ 8/25	.	14,050	....	8	35	..	57		
7/ 9/25		.. ..	....	14	48	..	33		
7/15/25	..	9,000	....	11	48	..	27	5	1
7/25/25	.	.....	....	31	59	..	..	9	1

**Case VII.**—M. S., age twelve. The patient was a school-boy. On admission he was suspected of having typhoid fever. The onset of his illness was with malaise and fever and indefinite localizing symptoms. Physical examination showed generalized lymph node enlargement. The spleen and liver were enlarged and palpable. There were no spots on the skin. His temperature was constantly elevated for five days. At times it was as high as 103.3° F. It gradually receded to normal. x-Ray pictures showed enlargement of the mediastinal lymph nodes. Urine analyses were negative.

The blood counts were as follows:

Date.	Hb.	R. B. C.	W. B. C.	Poly.	Lymph.	Mon.
6/5/00	80	4600	7000	26	70	4

**Case VIII.**—A. W., age twenty-four, admitted April 30, 1929, discharged May 27, 1929.

The onset of her illness was with "hives." There was no history of food indiscretion or eating shellfish and no history of taking drugs of any kind. She had headache, chilly sensations and pain over the small of the back and in the joints. Physical examination showed the cervical and axillary lymph nodes to be enlarged, the largest being about 0.5 cm. in diameter. The liver was enlarged. Her temperature varied from normal to 102° F. for twelve days and then remained normal. Bile was present in the urine on two occasions.

The blood counts were as follows:

Date.	Hb.	R. B. C.	W. B. C.	Poly.	Eo.	Bas.	Lym.	Mon.
5/ 3/29	13.5	4760	19,800	17	..	..	29	52 Platelets abun.
5/ 4/29	....	....	26,700	7	..	..	31	62
5/ 6/29	...	....	28,600	3	..	.	35	62
5/ 7/29	.. .	....	36,100	7	.	..	23	70
5/ 8/29	....	...	34,100	3	.	.	19	78
5/ 9/29	14.9	4200	28,800	7			8	85
5/10/29	....	....	28,200	9	1		11	79
5/13/29	...	. .	24,400					
5/14/29	....	. .	20,000	10			55	35
5/16/29	..	. .	16,400	7			63	30
5/18/29	. .	...	12,400	7			49	43
5/20/29			11,500	21	1		56	22
5/22/29		.	9,200	16			76	8
5/24/29	.	.	7,600	11		1	65	24

**Case IX.**—J. B., age twelve, admitted May 22, 1928, discharged June 1, 1928.

The patient was a schoolboy. The onset of his illness occurred on May 20, 1928, with pain and swelling below the angles of the jaw. The physical examination showed an acute adenitis and a nonexudative tonsillitis. The lymph nodes were discrete, fairly-firm and quite tender. The spleen was palpable. The axillary and inguinal lymph nodes also were palpable. His temperature for three days varied from normal to 103° F. Urine analyses were negative.

The blood counts were as follows:

Date.	Hb.	R. B. C.	W. B. C.	Poly.	Eo.	Large lymph.	Lymph.	Mon.
5/22/28	12.5	4480	7,800					
5/23/28	...	...	11,400	15	..	4	40	4
5/24/28	..	....	9,400	21	..	30	49	
5/26/28	..	...	8,800					
6/ 1/28	.		7,300	19	1	7	71	2

**Case X.**—E. B., age thirty-one, admitted July 19, 1928, discharged July 29, 1928.

For a week preceding the onset there were tenderness and slight enlargement of lymph nodes under the angles of the jaws. The onset was with sore throat. The physical examination showed both tonsils red, swollen and covered by follicular white exudate. There was bilateral enlargement of the anterior cervical lymph nodes, varying in size from 0.5 to 0.75 cm. The spleen was enlarged, firm and palpable. The liver was increased in size, it was palpable about 3 inches below the average normal level. The patient had a fever for six days varying from normal to 104° F. Urine analyses were negative.

The blood counts were as follows:

Date.	Hb.	R. B. C.	W. B. C.	Poly.	Eo.	Bas.	Lymph.	Mon.
7 20 28	14	4600	18,000	13	..	1	73	13
7 21 28			19,300	11	1	..	58	30
7 28 28	13	4370	9,900	28	1	1	59	11
8 20 28	13	4300	13,200	62	..	..	19	19

**Case XI.**—J. F. W. developed infectious mononucleosis as a complication of his convalescence from an operation for hemorrhoids. The data are incomplete.

The blood counts were as follows:

Date.	Hb.	R. B. C.	W. B. C.	Poly.	Lymph.	Mon.	Eo.	Bas.
10/ 3/34	80	4250	6,400	21	73	15	..	1
10/ 5/34	..	....	6,800	26	48	18	6	2
10/ 6/34	80	....	4,400	24	46	28	..	2
10/ 7/34	..	....	5,100	29	64	5	1	1
10/ 8/34	80	....	6,100	42	35	21	2	
10/ 9/34	80	....	6,300	41	50	8	..	1
10/10/34	80	....	6,500	30	64	15	..	1
10/14/34	..	....	7,600	31	57	9	.	3
11/16/34	..	.. .	8,800	54	42	4		
1/21/37	..	....	11,100	59	38	3		

**Case XII.**—Miss J. B. Patient was a twenty-year-old college girl who became ill on December 27, 1936, with malaise, sore throat, and fever, and generalized aches and pains. Two days later, when seen at her home her temperature was 101.2° F. Her pharynx was very red. The tonsils had been previously removed, and there were small palpable nodes in both posterior cervical chains and in the angle of the jaw on either side. Her chest was entirely clear, her heart was not enlarged. There were no heart murmurs. The abdomen was soft, the liver and spleen were not felt. The extremities showed nothing abnormal. The fever remained in the neighborhood of 101° F. for three days, then gradually subsided by January 7, 1937. During this time the lymph nodes became much more prominent, then gradually subsided. The spleen also became palpable. The blood counts for this period were as follows:

Date.	Hb.	R. B. C.	W. B. C.	Poly.	Lymph.	LL.	Mon.	Eo.	Bas.
12/31/36	..	....	3,500						
1/ 4/37	..	....	4,000	68	24	1	7		
1/ 6/37	80	4690	11,600	38	61	4	7	1	
1/ 9/37	..	....	11,700	16	74	9	2		
1/16/37	85	5450	10,200	16	75	3	3	1	2

She returned to college on January 19, 1937, whereupon her fever recurred and reached 99.3° F. She was seen again on January 25, 1937, when the blood count was:

6400            21            72            2            5            1

The lymph nodes in the neck were very much smaller and the spleen was no longer palpable. After remaining in bed for two days the temperature became normal again and she again returned to college. The temperature remained normal.\*

#### DISCUSSION

Infectious mononucleosis occurs more frequently in young adults. Intrinsically the disease is of importance because of its resemblance to the extremely serious condition, lymphatic leukemia, rather than in itself, since it is very rarely fatal and leaves no residual incapacity.

The spleen and lymph nodes usually are enlarged. In the severe cases the liver is increased in size and there may be jaundice. Aside from the resemblance to an ordinary upper respiratory infection the outstanding findings are in the blood picture. This shows as a rule an increase in the total number of leukocytes with a disproportionate percentage of mononuclear cells. This term, "mononuclear," should be understood as referring to morphology rather than to the existence of an excess of so-called "monocytes." In other words, the excessive percentage of single nucleated cells may resemble more the lymphocyte. In the exceptional case the total leukocyte count may not be above 10,000 per cubic millimeter.

Most patients show no abnormality in smears from the

\* Reported through the courtesy of Dr. Lawrence S. Carey, 1 Cedar Lane, Highland Park, Pa.

blood for any considerable time after recovery. In the severe cases, however, the presence of immature lymphocytes may persist for a long period. Many of the cases reported here have been followed, and in none of them was there any tendency to develop leukemia. In Case V, immature lymphocytes could be recognized ten years after apparent recovery.

Ulcerations in the mouth cavity and throat may occur but, as a rule, the sore throat complained of shows only congestion of the mucous membrane. Vincent's spirillae are seen in the smears from the throat in many cases but probably this organism is a secondary invader and not concerned in the etiology of the disease. Weak gentian violet solution or a solution of sodium perborate is useful for local treatment of the throat and mouth lesions.

Lymphadenopathy may be generalized but most often the cervical nodes are most prominent. The enlargement of the lymph nodes persists during the period of fever and then completely subsides. In none of the cases reported was there any evidence of nephritis.

The fever as a rule is not high but inclines to be more persistent than that observed with an ordinary upper respiratory infection. The tendency to persistence of an evening rise of temperature may be a source of worry to the patient's family and an embarrassment to the physician. In the exceptional case the temperature may rise to 105° F. An average duration of fever is difficult to arrive at. There was a variation from three days to three weeks in the cases I have observed.

The existence of jaundice means, as a rule, that the case is more severe than the average. The mediastinal lymph nodes may be enlarged as shown by fluoroscopic examination of that region.

### SUMMARY

Twelve cases of infectious mononucleosis are reported with some review of recent literature on this subject.

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## CLINIC OF DR. RALPH M. TYSON

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#### PROBLEMS IN INFANT FEEDING

GREAT progress has been made during the last ten years in the ability of the physician to feed infants satisfactorily. It seems that this improved ability on the part of the physician to feed infants successfully on artificial feeding has caused us to forget the significance of breast feeding in the development and well-being of the infant.

In these times of stress and strain on the part of mothers in a certain economic group, there has been a growing tendency to refuse to nurse their infants on the breast. The excuses offered are many and varied. Undoubtedly the attitude of the obstetrician, and the knowledge or lack of it on the part of special obstetrical nurses, has a great deal to do with the success or failure of breast feeding in this class. A few years ago Dr. Grulee of Chicago, with several of his assistants, presented some very valuable records in reference to the morbidity and mortality in breast-fed and bottle-fed infants.

TABLE 1

MORBIDITY AND MORTALITY; BREAST-FED vs. BOTTLE-FED

	Cases.	Per cent.	Morbidity.
Breast-fed .....	9749	48.5	37.4
Breast and bottle.....	8605	43	58.8
Bottle-fed.....	1707	8.5	63.6
Total cases.....	20,061		
Total deaths.....	218		
Breast-fed .....	15	6.7	
Breast and bottle .....	59	27.2	
Bottle fed .....	144	66.1	

Table 1 summarizes some of these differences in a very clear way. It tells a story that we need to emphasize over and

over again. Those of us who have had experience with newborn babies believe sincerely that most of the mothers can nurse their babies if they only would be willing to make a satisfactory effort. It can be clearly seen how the morbidity increases as the number of breast-fed babies in the group decreases. It can be readily seen that the mortality rate is ten times as high in those that were bottle-fed exclusively as in those who were breast-fed exclusively. Statements have been made from time to time regarding the greater resistance to disease that the breast-fed infant has, but our teachings have not been as effective as they might be for doctors, the nurses and mothers. It should be clearly understood what it means to the child to wean it from the breast.

In these days of simplified infant feeding there is not much question about the success of formula feeding. At the present time the exact needs of the individual child for the several food elements are quite definite. Enough scientific studies have been made to prove these statements and the data which follow:

TABLE 2

## BASIC NEEDS IN INFANT FEEDING (MINIMUM REQUIREMENT)

						Calories.
Fat...	2	Gm. per pound per day	$\times 9.3$	=	18.6	
Protein...	1.5	" " " " "	$\times 4.1$	=	6.1	
Carbohydrates...	5.0	" " " " "	$\times 4.1$	=	20.5	
						45.2

Whole milk  $1\frac{1}{2}$  ounces contains { Fat, 2 Gm.  
Protein, 1.5 Gm.  
Carbohydrates, 2 Gm.

Sugar added, 1/10 ounce per pound per day.

It has been shown that the basic needs of the growing infant are 2 Gm. of fat,  $1\frac{1}{2}$  Gm. of protein and 5 Gm. of carbohydrate per pound per day. This is necessary to meet the minimum requirements of the average infant. In caloric values this amounts to 45 calories per pound. It is doubtful if any infant will grow on less than 45 calories per pound per day, and these calories should be secured by the above arrangement of the necessary food elements, so that fat makes up about 35 per cent, protein 15 per cent, and carbohydrates 50 per cent of the total caloric need.

To put these figures into terms that can be easily understood by the parent, it is known that  $1\frac{1}{2}$  ounces of whole milk contains 2 Gm. of fat,  $1\frac{1}{2}$  Gm. of protein, and 2 Gm. of carbohydrate. The amount of carbohydrate is inadequate to what is believed necessary, so the 3 additional Gm. of carbohydrate must be added to the formula. This amounts to  $\frac{1}{10}$  of an ounce of sugar per pound per day.

TABLE 3

MINIMUM AND MAXIMUM REQUIREMENTS PER POUND OF EXPECTED WEIGHT

Whole milk.....	$1\frac{1}{2}$	up to 2 ounces
Sugar.....	$1/10$	up to $\frac{1}{8}$ ounce
Fluids.....	3	up to 2 ounces
Calories .....	45	up to 60 cal.

Quite a large number of babies will not grow satisfactorily on the minimum requirements as stated, and it is necessary to increase the amount of milk up to 2 ounces and the amount of added sugar up to  $\frac{1}{8}$  of an ounce per pound per day. This increases the caloric values up to 60 calories per pound per day. The average young infant will need about 3 ounces of total fluids per pound per day. This amount of fluids gradually decreases during the first year of life.

TABLE 4

ENERGY REQUIREMENTS (DISTRIBUTION)

Basal metabolism (resting).....	25	calories per pound.
Activity.....	10	" " "
Growth.....	7	" " "
Unutilized food.....	6	" " "
Specific dynamic action.....	4	" " "

#### Variation

Low in first few weeks:

First to fourth months.....	50 to 60	calories per pound
Fourth to eighth months.....	45 to 50	" " "
Eighth to twelfth months.....	40 to 45	" " "

The energy requirements of the average infant are stated in Table 4, and are distributed according to the specific needs of the child and include basal metabolism, activity, growth, unutilized food and specific dynamic action of food substances,

with particular reference to proteins. There is considerable variation in the energy requirements of infants during the first year. It is highest during the first four months, and decreases toward the end of the first year. The needs of the infant during the lying-in period are particularly low. It is this fact that has convinced most of us who deal with the newborn that the full caloric requirements of the newborn baby should not be met. There should be a gradual increase in the amount of food offered to the infant in this period. Shortly after the newborn period, the greatest amount of food is required. This is the period in which we have the most rapid growth.

In Table 5 some approximate measures of five different types of carbohydrates are given. It is to be remembered that

TABLE 5  
APPROXIMATE REQUIREMENTS; SUGARS

Cane sugar . . . . .	1 ounce equals 2 level tablespoonfuls
Karo syrup . . . . .	1 " " 2 " "
Lactose . . . . .	1 " " 3 " "
Dextrimaltose . . . . .	1 " " 4 " "
Mellin's food . . . . .	1 " " 4 " "

The caloric values of sugar are all the same.

#### Caloric Values

	Calories.
1 ounce any sugar yields . . . . .	120
1 ounce whole milk yields . . . . .	20
1 ounce skimmed milk yields . . . . .	10
1 tablespoonful cereal yields . . . . .	25

the caloric values of these sugars are the same. The caloric values of whole milk, skimmed milk and cereals may be found in this table.

To feed young infants according to the method previously described does not always mean that these same infants will do well. It is to be remembered that cow's milk is not so readily digested as is breast milk. This is probably more a mechanical problem than it is a chemical one. It is felt at the present time that the difficulty in digesting cow's milk is due to the large, tough curds that are formed in the stomach and the difficulty that the digestive juices have in penetrating these curds.

Table 6 outlines five ways that aid materially in the ability of the child to digest cow's milk. It is obvious, of course,

TABLE 6

## AIDS TO DIGESTION OF COW'S MILK

1. Diluting with water.
2. Diluting with cereal water.
3. Boiling for three to five minutes.
4. Addition of alkalis.
5. Addition of acids.

All methods concerned with producing softer and smaller curds.

that if too much dilution with water is attempted, the total quantity of the formula used will prohibit the giving of sufficient calories to meet the needs. All of the methods shown in Table 6 are concerned mainly in producing smaller and softer curds. The addition of cereal water has an added advantage in changing the formula to a colloid solution. It seems that the intestinal tract is better able to digest such solutions than it is crystalloid solutions. It is the practice of most pediatricians to boil all milk that is given to young infants, feeling that this is necessary not only to inhibit the large, tough curd formation but also to insure a sterile solution. The use of alkalis has to a large extent gone out of vogue, for it is now known that many young infants do not have sufficient hydrochloric acid for their own digestive needs, hence the use of alkalis should be limited to those cases in which a hyperacidity appears to be present. In such circumstances remarkable success in the feeding of difficult cases can be secured.

The common acids that are used are the U. S. P. lactic acid, about 2 drops per ounce of milk in the formula; citric acid as found in orange and lemon juices, requiring about 1 ounce of orange juice or  $\frac{1}{2}$  ounce of lemon juice for the total formula each day. The addition of these acids has revolutionized infant feeding, particularly in the difficult cases and in the malnourished infant. In the last few years the use of evaporated milk has in many places supplanted fresh certified milk. It is to be remembered that 1 ounce of evaporated milk is equivalent to 2 ounces of fresh milk in caloric values.

TABLE 7

## FEEDING THE NORMAL NEWBORN

1. No cow's milk in the first two or three days.
2. Begin with smaller amounts—weaker dilutions.
3. Wait for favorable signs before increasing.
  - No vomiting.
  - Hunger.
  - Normal stools.
4. Then increase slowly, taking ten to fourteen days to reach normal requirements.

## Example

Whole milk.....	7 ounces—8—9—10—11
Lactose.....	1 level tablespoonful—2—2½—2¾
Boiled water.....	14 ounces—13—12—11—10
7 bottles of 3 ounces—feed every three hours.	

Specific problems in infant feeding will arise from time to time for the general practitioner and the pediatrician. Feeding the normal newborn infant is such an important problem and so frequently misunderstood that it seems wise to emphasize some important points in such procedure. It is the author's opinion that no cow's milk, or very little, should be given in the first two or three days of life. It is always wise to begin with smaller amounts and weaker dilutions during this period, and to wait for favorable signs, such as no vomiting, hunger, and the appearance of normal stools, before increasing the amount of cow's milk. Increases should be made slowly, over a period of possibly from seven to fourteen days, before reaching the full caloric requirements of the infant in question. It seems wise not to provoke indigestion in the newborn infant, and to guard the normal physiologic functions of the gastro-intestinal tract even at the expense of weight loss or slow weight gain. It is much easier to prevent indigestion than it is to overcome it in the very young infant. It does not seem wise to the author to institute cow's milk feeding in the first two or three days before the mother's milk has appeared in the breasts. Complementary feedings should not be given to breast-fed babies until sufficient time has elapsed to see whether the baby can be successfully breast-fed. If the weight loss continues, however, and exceeds 10 per cent of the birth weight, additional food must be given under these

circumstances. It is the author's opinion that adequate amounts of water, with perhaps a weak dilution of carbohydrate, are all that is needed by the average newborn baby in the first two or three days after birth. It is perfectly true that when a young infant is started on a formula such as shown in Table 7, it will not take all of the 3 ounces at every feeding. It is allowed to take as much of the amount specified as it seems to desire. Attempts are not made to force extra feeding on these young infants.

After an experience in dealing with about 20,000 newborn babies that have been under the author's supervision in the past twelve years, I have come to the conclusion that this method of feeding the newborn is a highly satisfactory and safe procedure. Of course, it goes without saying that newborn babies differ decidedly in the amount of food they will take and the amount that they are able to digest. This method will feed fully 90 per cent of all the normal full-sized newborn infants.

In Table 8 the problems in feeding the premature child are expressed. It seems to be the universal opinion that the best

TABLE 8

FEEDING THE PREMATURE CHILD BY BOTTLE—BRECK FEEDER—DROPPER OR TUBE

1. Water 1 to 4 ounces every three hours—first day
  2. Breast milk best of all foods.  $\frac{1}{2}$  to 1 ounce every three hours.
  3. Skimmed milk..... 8 ounces  
     Lactose..... 1 tablespoonful  
     Lactic acid..... 16 drops.  
         Offer up to 1 ounce every three hours.
  4. Similac . . . . . 3 tablespoonfuls  
     Boiled water..... 8 ounces.  
         Offer 1 ounce every three hours.
- Favorable signs:* No vomiting, no distention.  
                     Normal stools—hunger.  
                     Increase quantity—quality.  
                     Add cream slowly.

food for the premature child is breast milk, which should be given either by bottle, Breck feeder, medicine dropper, or by gavage. Very few premature children are ever put to the breast during the first week of life. In the first twenty-four hours,

water or a weak carbohydrate solution is all that is necessary. If breast milk can be secured, 1 to 4 drachms may be given every three hours. In the absence of breast milk the use of skimmed lactic acid milk, with added sugar, has proved very successful. Some of the powdered milks, such as Similac, have proved very useful in such cases. It is more important in premature infants to wait for favorable signs, such as no vomiting, no distention, the appearance of hunger, and normal stools, before increasing the quantity and quality of the formula.

In Table 9 there is a satisfactory formula for feeding a normal three-month-old child that weighs 12 pounds. It is

TABLE 9

## FEEDING NORMAL THREE-MONTH-OLD CHILD WEIGHING 12 POUNDS

		Calories.
Whole milk.....	21 ounces	= 420
Lactose.....	4½ tablespoonfuls	= 180
Barley water..	9 ounces	—
		12)600
		50

6 bottles of 5 ounces—Feed every three hours. 6—9—12—3—6—10

Another way of expressing it:

	Calories.
50 calories per pound . . . . .	12 × 50 = 600
Sugar ½ ounce per pound . . . . .	1½ × 120 = 180
Difference.....	420
420 calories divided by 20 = 21 ounces milk.	

noted that 1¾ ounces of whole milk per pound body weight, and ⅓ ounce of lactose are given, using barley water as a diluent in this case to secure a colloid solution. The amount of barley water used is small and scarcely enters into the caloric values. It is estimated that this child should receive about 50 calories per pound. The amount of food at a feeding that a child can take without disturbance is about 2 ounces more than it is months old, up until the child is six months of age. Using this same principle, a formula can be easily calculated for any normal infant regardless of its age and weight.

In Table 10 a formula for a vomiting baby weighing 7 pounds is suggested. Of course, under such circumstances a diagnosis of pyloric obstruction should be anticipated, but until a proper diagnosis can be made this formula of skimmed



TABLE 10

FORMULA FOR VOMITING BABY WEIGHING 7 POUNDS

		Calories.
Skimmed milk.. . . . .	16 ounces	$\times 10 = 160$
Lactose.. . . . .	3 level tablespoonfuls	$\times 40 = 120$
Farina. . . . .	2 level tablespoonfuls	$\times 25 = 50$
		<u>7)330</u>
		47

Cook farina in milk two hours.  
 Evaporate to 12 ounces.  
 Add sugar.  
 Divide into 6 bottles of 2 ounces each.  
 Feed every four hours.

milk, lactose, and farina can be used to advantage. It is important to cook the farina for a two-hour period and evaporate the skimmed milk to about 12 ounces total quantity. It seems wise to feed smaller amounts than usual and at four-hour intervals under such circumstances. The cream is omitted because it is probably the hardest of the various food elements to digest, and we believe is the last to leave the stomach. It has been demonstrated that the stomach of the child can grasp the thick cereal feeding much better than it can the thinner used formulae and that vomiting will not be as severe. This formula, combined with atropine or phenobarbital in proper doses, will give you a starting method of handling the child who is vomiting and in whom you suspect some pyloric obstruction. It is well to remember that a vomiting child is usually in a state of water deficiency. The administration of normal saline solution subcutaneously is very advantageous in the handling of these cases.

In Table 11 a formula for feeding the malnourished child

TABLE 11

FEEDING THE MALNOURISHED CHILD

Based on expected—not the actual weight) four months old weighing 8 pounds

		Calories.
Whole milk . . . . .	24 ounces	$\times 20 = 480$
Lactose . . . . .	4 level tablespoonfuls	$\times 40 = 160$
		<u>8)640</u>
Bottle water . . . . .	6 ounces.	
Inf. oil . . . . .	48 drops.	80
5 bottles of 6 ounces each—Feed every four hours.		

is given. The formula is based on the expected rather than the actual weight of the child. The case in question is a four-month-old child weighing 8 pounds. The expected weight of such a child would be about 14 pounds. In such circumstances lactic acid whole milk with added lactose is used. When based on the actual weight it is noted that this child receives 80 calories per pound, but when based on the expected weight of 14 pounds it amounts to about 45 calories per pound. The lactic acid is used in this formula because so many of the malnourished infants have an insufficient quantity of acid in their stomachs. This aids materially in making the formula more digestible. In feeding the malnourished, the formula is not the entire problem in all the cases. In some the reason for the malnutrition may be found if a careful examination of the child is made. Chronic diseases such as tuberculosis and syphilis must be ruled out as etiologic agents. Some acute infections of the upper respiratory tract, the urinary tract, and the gastro-intestinal tract must be searched for. Quite a large number of malnourished children are in such a condition because of some congenital anomaly of the heart or some other vital organ. If your child does not progress on the above formula, do not blame the formula but look for the specific cause for the malnutrition.

In feeding the acutely sick infant, a few very important facts should be kept in mind. The appetite has been lost, its digestive capacity lessened, the digestive enzymes are less in amount and less active. It is wise to remove cream from the milk that is used. The amount of sugar should be reduced. If possible, maintain the required fluid intake. If the nose is obstructed by congestion, it is wise to feed by spoon or a medicine dropper. As soon as an infant becomes ill these general principles should be put into effect.

In Table 12 some general principles are given for feeding the child who has *diarrhea*. A *starvation period* should be given the infant of from six to twenty-four hours, but no longer, except in unusual circumstances. During the starvation period, fluids such as water, barley water, weak tea, and fruit juices should be given, trying to keep the fluid intake up to or slightly above normal. A good starting formula for such an infant consists of skimmed milk and barley water, equal

TABLE 12

## FEEDING THE CHILD WHO HAS DIARRHEA

Starvation period.....	Six to twenty-four hours—no longer.						
Fluids during starvation—	Water, barley water, weak tea and fruit juices.						
Starting formula.....	<table> <tr> <td>{ Skimmed milk.....</td><td>12 ounces.</td></tr> <tr> <td>{ Barley water.....</td><td>12 ounces.</td></tr> <tr> <td>{ Dextrimaltose.....</td><td>1 tablespoonful</td></tr> </table>	{ Skimmed milk.....	12 ounces.	{ Barley water.....	12 ounces.	{ Dextrimaltose.....	1 tablespoonful
{ Skimmed milk.....	12 ounces.						
{ Barley water.....	12 ounces.						
{ Dextrimaltose.....	1 tablespoonful						
6 bottles of 4 ounces—	feed every four hours.						

parts, with a small amount of dextrimaltose. This formula should be continued for several days, waiting for favorable signs before increasing its strength. The favorable signs are decreased frequency in the number of stools, and a tendency to become more formed. As soon as such signs are present the formula may be increased in strength, gradually adding cream and increasing the carbohydrate.

Associated with diarrhea is another condition which we are so apt to forget, namely, a change in the water balance and acid-alkali relationship. These changes are most important and demand early recognition and prompt treatment, otherwise fatalities may occur. There was a time in the history of infant feeding when diarrhea associated with a toxemia could destroy a child in a twenty-four-hour period. It was spoken of as "milk poisoning." We believe now that it is more than likely due to chemical changes that have taken place in the body. This chemical change is spoken of as "acidosis."

In acidosis the pH of the blood is below the normal of 7.35 to 7.45. The neutral hydrogen ion concentration gives a pH of 7. Anything below that is on the acidotic side and anything above that is on the alkalitic side. Another way of determining changes in the electrolytic balance is the estimation of the CO<sub>2</sub> combining power of the blood. Normally this is from 40 to 60 volumes per cent. An alkalosis is anything above 60 volumes per cent, and an acidosis is anything below 40 volumes per cent. The blood is slightly alkaline at a constant level, although acids are being formed all the time. The acids are neutralized by the excess of base, including carbonates, phosphates and proteins, or some is lost by the lungs as CO<sub>2</sub> in the expired air; the kidneys are able to secrete organic and mineral acids and also have the ability to break up urea, so liberating ammonia, which will help to neutralize

excess acids formed in the body. By these various mechanisms the body is able to maintain the blood at a constant level of slight alkalinity. In the presence of diarrhea and certain other diseases these normal methods of neutralization are insufficient to make proper adjustments. In diarrhea there is an excess loss of base from the body when large amounts of digestive juices are secreted to overcome the diarrhea. In diabetes and starvation there is an abnormal production of acids in the body. In extensive pulmonary disease proper elimination of  $\text{CO}_2$  is interfered with. In nephritis the kidney is unable to perform its proper functions of elimination or neutralization of acids. It is by paying particular attention to these features that cases of diarrhea can be easily managed. In some of the cases of acidosis associated with diarrhea and other conditions, the mucous membranes of the mouth have a cherry red color. An acetone odor to the breath may be noted. There is nearly always hyperpnea, the respiration sometimes reaching 80 to 100 per minute. The skin has lost its elasticity and when pulled up in a fold is very slow returning to its normal state. This is spoken of as "dehydration of the tissues." Even though the body has a large storehouse of fluids in reserve in the various tissue spaces, a profuse diarrhea and especially if associated with vomiting, will drain this reserve in a very short time. This must be replenished promptly or a fatality may result. The treatment consists of giving normal saline and 10 per cent dextrose by mouth, by rectum, by vein, or into the peritoneal cavity. Normal saline solution or Hartmann's solution subcutaneously is very advantageous.

In Table 13 an outline is given for vitamin feeding. Whether a child is breast-fed or bottle-fed, these vitamins should start at one month of age. It is wise to begin orange juice with small amounts well diluted in water, and increase as rapidly as possible so that the child is getting at least 2 ounces of orange juice by the time it is three months of age. Cod liver oil, supplying vitamins A and D, should be started in small amounts, preferably from a dropper or spoon, and increasing slowly so that the infant gets 3 teaspoonfuls of cod liver oil by the time it is five or six months of age. Sunshine, not necessarily direct, should be secured for the infant. Two to four hours daily in the open air should be part of the reg-

TABLE 13  
VITAMIN FEEDING

Orange juice At 1 month—Vitamin C—1 teaspoonful to 2 ounces.  
Cod liver oil At 1 month—Vitamins A and D—10 drops to 3 teaspoonfuls  
Sunshine... Two to four hours daily.

## Additional Foods

- At 4 months start vegetables.
- At 5 months start cereals.
- At 6 months start egg yolk.
- At 7 months start fruit pulp.
- At 8 months start puddings.
- At 9 months start zwieback.
- At 10 months start egg white.
- At 11 months start meat.

imen for each infant. Additional food, such as vegetables, cereals, egg yolk, fruit pulp, puddings, zwieback, egg white and meat, may be started approximately as indicated in Table 13. The beginning of these additional foods will depend on the circumstances of the individual case. They may vary, depending on the needs. In case of constipation, fruit pulp may be started first. In case of developing anemia, the iron-bearing foods or vegetables, and preferably pabulum, may be started first. As soon as teeth appear, some hard substances, as crust of bread or dry toast or crisp bacon, should be instituted. The child should be taught to chew as soon as possible. It is always wise, in feeding these additional foods, to begin with extremely small amounts, increasing as tolerance is developed. The mother should be cautioned not to be annoyed or disconcerted if the infant first refuses these additional foods. Constant repetition of these feedings by an unemotional mother is bound to correct the difficulty in a relatively short time. The canned commercial vegetables seem to be well adapted for infant feeding.

In Table 14 are listed the types of stools that may be expected in the infant. It is well to have a clear understanding of these stools, and it is particularly well to remember that there is a close analogy between the starvation stool and meconium, and to remember that the starvation stool is not an indication for further reduction of the formula as one would in diarrhea, but is a clear indication for an increase in the

TABLE 14

## TYPES OF STOOL EXPECTED

Meconium.....	Brown, tarry, during first three days.
Transition.....	From third to sixth day, mucus, brownish-yellow curdy.
On breast milk...	Liquid, yellowish—acid, 1 to 5 daily.
On cow's milk...	Formed, yellowish, putty—alkaline, 1 or 2 daily.
Additional foods.	Colored by vegetable used.
Starvation stool.	Greenish, loose, mucus, 2 to 5 daily.

amount of food, if the general situation is satisfactory. It is well to remember that the transition stool, which occurs on the third to the sixth day of life, is a sign of gastro-intestinal irritation and in many cases of inflammation. It is during this period that breast feeding is indispensable, but in case of artificial feeding a diluted formula is advisable.

The first year of life should be a period of training for the child. It should learn how to suck from the breast, to suck from a bottle, to eat from a spoon, to drink from a glass, to chew hard foods, to like and digest milk, cereals, vegetables, eggs, meats, fruit juices, and cod liver oil, without coaxing, urging, or entertainment during mealtime.

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#### UNDERNUTRITION IN CHILDREN

IN the later conception of undernutrition in children we find many changes from the ideas even of fifteen or twenty years ago. Pediatricians are swinging away from the hard and fast rules of height-weight tables. Even the more recent tables of sitting height and of shoulder width and hip width-height ratios are tempered by consideration of the individual and of his family characteristics.

Certainly we are no longer concerned with weight alone. Any survey of an individual's state of nutrition must include: the rate of growth, the firmness of the muscles, the posture, presence or absence of anemia, the ability to maintain physical and mental effort, the degree of nervous fatigue as indicated by nervous irritability, whining, easy crying, etc., the individual's resistance to infection, and dental caries.

In other words there is no one measure of the state of nutrition when considered in the broad sense. We must take the complete picture. I do not mean that a child who shows only one of the above-mentioned criteria is suffering from undernutrition, but a child showing a fair proportion of them is undernourished.

In the practice of medicine our problems are how to correct the condition and how to prevent its occurrence.

Undernutrition is rarely, if ever, a primary condition. There is always some underlying factor, although in many cases it is impossible to uncover the actual cause and we are limited to symptomatic treatment.

Under etiology we can place a long list of conditions, most of which are subdivisions of the following:

Diet.

Infections.

Anemia.

Psychic or neurologic disturbances.

Endocrine disturbances.

Heredity.

It is impossible in an article of this scope to follow out all the ramifications of the various etiologic factors. Moreover, it is our wish to be of practical help in this problem, so we will confine the discussion to the boundary of practical medicine and of common sense.

Let us remember, when considering the question of diet, that we are concerned not only with what goes into the child but with what becomes of the ingested foodstuffs.

Here again we are confronted with the variation of the individual. A 1928 automobile can be driven quite successfully with a low-price gasoline which would give very poor results in a modern high-compression motor.

So it is with our diets in nutrition problems. One child can absorb and utilize one type of food readily, another gets no benefit from that food. One child needs to be fed small amounts frequently, another needs to cut out his between-meals snacks. There is no rule. These questions must be worked out for each individual.

We can further extend our comparison to the automobile. If a car is run at high speed there is a greater demand for fuel, lubrication and water. So with humans, the individual putting out great effort, either nervous or physical, requires a greater energy intake than one at rest. Furthermore, the problem is complicated by the question of nervous fatigue causing anorexia or faulty digestion and metabolism. It does no good to push food into an exhausted child who cannot digest it or can absorb it only poorly.

It is evident, then, that faced with a case of undernutrition we must study that case as an individual. As a practicing, and I like to think practical, physician, I am overcome with envy when I read the works of some authors, and see the painstaking and detailed studies they have made on some of their cases. We are usually confronted with a case requiring study, or one which would be interesting to study, but the



family have no financial ability and often no desire to undergo such protracted efforts to arrive at the truth. In practice such cases come into one's office with a finally anxious mother in search of a "tonic" that will put on pounds in a few days. I wish to heaven it were as simple as they think, and as some of the detail men from commercial houses would have us believe. If we believed the claims some of them put out you could expect to anoint your hardwood desk chair with their preparation and have it turn into an overstuffed sofa. Unfortunately the road to good nutrition is too often as hard to traverse as the road to knowledge.

When these cases come into your office you have to start with a complete history—the individual's history starting with its term *in utero*, and the family history going back, as usual, two or maybe three generations.

Was the delivery normal, protracted, precipitate, instrumental? Was the neonatal period normal or complicated? What was the early feeding history, the condition of the bowel? The type of eating habits? What were the illnesses of infancy and childhood? Did any psychic factors develop? Any growing pains or other possible indication of latent rheumatic infection? Were any allergic symptoms manifested? Did any acute or apparently minor illness occur before the onset of the undernourished condition? Have respiratory infections been common? Has the child showed any signs of parasitic infestation? What type of appetite does the patient have? Is he hungry but quickly filled? Will he eat large amounts of things he likes? Does he eat between meals? Are his stools light-colored or soapy? Are they sour and fermentative? Are they constipated because of low intake or is the intake low because he is constipated? Is he gassy? Are the stools putrefactive? Is the child whining, crying easily, quickly exhausted? Does he feel better after eating? Which meal does he eat best? What methods have been previously used to quicken his appetite or to improve his nutrition? What has the growth and development curve done in previous years?

In the family history we must look for hereditary characteristics of growth, for allergic diathesis, for rheumatic tendencies, tuberculous contacts, endocrine disturbances, anemias, etc.

The social history should include the home and school environment, the family attitude, the sleeping conditions and the general hygiene.

Following the history comes a thorough physical examination. This should start with a general summary of the physique. Is the stature short, the bones small, are the legs, arms and trunk in proportion? Any craniotabes? Or evidence of rickets? How is the posture? What is the tone of the muscles? Any skin conditions? Any gross evidence of endocrine disturbance? Have the child lie flat and see if the abdomen is scaphoid in that position. Can he sit up from the recumbent position without help? Is there a diastasis of the recti? Any hernias? What about the secondary sex characteristics? Any sign of goiter or of myxedema? Make a careful examination of the nose and throat, and be suspicious of sinus infection when you see overgrowth of lymphatic tissue on the pharynx. Abscessed deciduous teeth may be a cause of anorexia, and loss of chewing teeth has been given as a cause for improper absorption of food. A low-grade gingivitis may explain a lack of appetite and of course the tonsils should be given a very suspicious inspection. Halitosis, so prominent in the advertisements of late, may be a result of postnasal drip from a low-grade ethmoiditis, from tonsillitis or may come from digestive disturbances with faulty gastric secretions. Cervical nodes may be a clue to a focus of infection and a suspicious thyroid with a rapid pulse may indicate a more serious condition.

The chest may be negative to the ear and to the percussing finger but in the face of failure to produce results after reasonable treatment or in the absence of other clues a tuberculin test and an x-ray are warranted. The abdomen may show visible peristalsis or palpable masses. It may be distended and tympanitic or flat and dull with a spastic cecum or sigmoid indicating an irritated bowel. You may be able to localize a point of tenderness in the right lower quadrant or lumbar region indicating a low-grade appendicitis. Nicholson<sup>1</sup> has reported a series of cases of mechanical lesions of the appendix, some of which showed remarkable improvement in nutrition after appendectomy. There may be significant

herniae. Sometimes the correction of flatfoot brings about remarkable changes in disposition and appetite.

Suppose our physical examination reveals nothing of significance, what more can we do, or what are we justified in doing, in the way of laboratory work? All cases should have a routine urine examination and most should have a blood count. A chest x-ray should be held in mind as should a stool examination. Both of these are important, but where expense is a factor can be held in reserve until the results of preliminary treatment have been observed. These cases require such a detailed history and physical examination because their etiology is so obscure, and because the younger children at least cannot give us accurate subjective symptoms.

When starting treatment on these cases I feel we should always take the parents into our confidence. Outline what we have found wrong and what we intend to do about it. If they are the worrying kind and feel that reassurance is worth the expense it is wise to have the various fundamental laboratory work done at once. As I stated before, I think all of these children should have a urinalysis and practically all should have a blood count. x-Rays can well be reserved unless the parents feel it essential. Personally I think an x-ray of the chest is the most important as it may give information not attainable by the ordinary physical examination. Gastrointestinal x-rays rarely give much information. Occasionally they will pick up a previously unsuspected megalocolon or redundancy of the bowel. After all, such things make little difference in the treatment. Even a latent tuberculosis in childhood would be treated exactly as we treat all malnutrition. A Mantoux is less expensive and in the younger children more definite than x-ray in diagnosis.

Where infection exists we must of course do everything possible to eradicate the focus. In my experience the most common focus is in the sinuses. As we all know, only too well, treatment of chronic sinusitis is disappointing. However, it must be remembered that infection and undernutrition set up a vicious circle which must be continuously and patiently treated from all angles.

Here again I wish to emphasize the factor of energy expenditure. We have all seen children with a good energy in-

take and failure to gain when infection is present. We may take this as definite evidence of the energy required to combat the infection, or lost because of the presence of infection. All parents complain when told the children must rest. Most of them will cooperate when the need is described in simple terms of energy intake and demand. The easiest is the analogy to a furnace with the drafts on and the windows of the house open. I put one patient to bed for three months. In two years she had failed to gain past 42 pounds. The first three weeks she gained very little, after that she gained steadily until she had put on 20 pounds.

Much has been written recently of the various elements of the diet. One can find almost any theory to have worked in the hands of various people. The chemical constituents and the vitamins have been much in prominence during the last few years.

Marriott, Jeans and Clausen<sup>2</sup> give an excellent brief discussion of the various chemical and vitamin factors. Marriott feels that the average diet contains sufficient amounts of sodium, potassium, magnesium, sulfur and chlorine. Calcium, phosphorus, iron and iodine may be deficient.

Jeans feels that too much iron added to the diet may be harmful and might even cause low phosphorus rickets. As a satisfactory dose he cites 5 mg. a day for children three to six months of age and 10 mg. for children six to twelve months of age. He points out that the much-vaunted spinach supplies little iron and that in large quantities may even rob the body of iron. Jeans also points out that the celiac diet, high in proteins and monosaccharide sugars and low in fats, frequently works wonderfully well in undernourished children not really in the celiac class. He feels that such a diet is more apt to increase weight than the small bulk, high fat diets which often are less readily utilized by the child.

Glassburg<sup>3</sup> puts his trust in urging the individual to greater caloric intake, making the diets as varied and attractive as possible. Most of his work was done with adults. He found a vitamin B concentrate fairly effective.

McCallum<sup>4</sup> feels that we are on the edge of still greater discoveries in the nutrition field. He quotes Rose of the University of Illinois as authority for saying that of the 22 known

amino-acids 9 are essential in the diet, 9 not essential and 4 are not yet sufficiently studied.

Clausen<sup>2</sup> cites the recent developments in work with vitamins. He feels that earlier administration of vitamins may prevent later hypovitaminosis.

Holt<sup>5</sup> and fellow workers have done an exhaustive piece of work on fat absorption. I was interested to see that they found a high mineral intake gave a lowered fat absorption. These workers also felt that atrophic infants were not able to absorb fat normally.

My personal feeling is that with a little effort and thought most, if not all individuals, can be given an adequate diet. I have found that most of my cases do better with a low fat diet. Many cases I have taken entirely off fat for a period and increased the protein and carbohydrate elements, using vitamin concentrates to supplement the diet. I feel that such a diet should not be continued over too long a period, as some of the unsaturated fatty acids seem to be essential elements of the diet. (Burr and Evans.<sup>6</sup>)

Some children with poor appetites will gulp down a glass or two of milk and eat practically nothing else. In such cases I feel we should take milk entirely out of the diet. The child's mother usually exclaims in horror that he will certainly starve. However, if we give meat twice a day and egg once a day with fair helpings of vegetables, throw in some calcium and keep up the liquid intake, after about a week their appetite for the general diet is markedly improved. Temporarily cereal may be given twice daily, but as a general rule I prefer only one cereal feeding when the child is on full diet. Such cases, if they do not actually lose weight, I will keep off milk a month or more and then add it in minimal amounts, usually 1 to 1½ pints a day. Frequently I attempt to aid digestion by using hydrochloric acid and possibly pepsin or caroid at mealtimes. I rarely use tonics of the usual strychnine variety. I feel that they stimulate the individual to greater activity and most of these children need to be held down rather than stimulated. In spite of my preference for low fat diets I have, in some cases, seen decided gain in weight where fat is added to the diet. This may be done with cod liver oil, but many of the older children hate it and are nauseated by it when given in

doses large enough to be of caloric value. I have had better luck with olive oil and corn oil. The latter possesses the advantage of being rich in unsaturated fats, and, according to Holt *et al.*,<sup>5</sup> the unsaturated fats seem to aid absorption of all the fats in the diet.

Where pronounced anemia is present and fails to respond to rest, diet, medication, etc., I feel that small transfusions should be used. This is rarely necessary except when infection is present or following severe infections.

The psychic factors are often discouraging to treat. "You can't teach an old dog new tricks" is an old and trite saying but it certainly applies to some of the anxious and neurotic mothers one meets in these cases. With older children school during the winter and camps in the summer will help in some cases. I once lost a friend and patient by telling such a mother her child would be all right when he was old enough to get away from her, but I was proved right. In younger children I have occasionally been driven to putting the child in foster home or convalescent home until the psychic element could be broken down. In nervous, highstrung children correction of minor eye defects is often of value.

The inherited types are possibly the most difficult. It may be due to a fault in the germ plasm. Possibly we would not be confronted with such cases if medical science had not developed ways of saving many of these infants. It may be that some of them are endocrine in origin. I have seen a few decidedly benefited by thyroid medication. We can be helped in this diagnosis by x-ray of the wrists and hands for the centers of ossification. Thyroid should be started in small doses,  $\frac{1}{10}$  grain, and worked up slowly.

Much has been written about the use of insulin in under-nutrition. Pitfield<sup>7</sup> originated this method and in his hands I have seen good results. Many writers have come out against it and many have found it of help. Ellenburg<sup>8</sup> recently reported its use in 10 cases. He felt that there was no remarkable gain in weight but a very definite change for the better in the general vitality and behavior of the children. Where insulin is to be used the child should be hospitalized.

Apparently most of the endocrinologists feel that the growth hormones, etc., are not yet sufficiently studied to be

useful in general work. I have had no personal experience with them, feeling that, as yet, such work is too experimental. Undoubtedly the time will come when we will be equipped with a potent weapon for use in the children showing a symmetrical but undersize physique and a small capacity for food.

In closing there are a few points I want to stress.

Rest, enforced if necessary, is an essential part of any treatment of undernutrition. With children rest is almost impossible unless they are kept occupied with games or other amusements. With a little ingenuity, much can be done to keep a child happy in bed. A bowl of puffed rice and a box of toothpicks can be made into interesting animals, houses, trees, etc. A platter or tray of corn meal will take the place of sand. Reading hours, erector sets, etc., can all be utilized for restful amusements.

Belts and braces for the correction of ptosis are usually disappointing. In any event they should be combined with exercises to strengthen the muscles they are designed to support.

Nutrition is difficult to maintain in the presence of infection, and infection is difficult to eradicate in the presence of undernutrition. The two are very apt to be found together so both must be treated.

Tonics may be used but must not be abused. You can whip a tired horse all day and he can't go any faster.

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## CLINIC OF DR. P. S. PELOUZE

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### PSYCHOGENIC SENSORY AND FUNCTIONAL UROGENITAL SYMPTOMS

THE extent to which the mind plays a part in the development or continuation of sensory and functional symptoms of the urogenital tract is not realized even by one who devotes years to urologic study. For no sooner does he get the idea that he at last has become really conversant with the matter than an entirely new and previously unsuspected field opens to him.

It is probable that no organs or functions of the human body are more dependent upon a proper psychoneural balance than are those of the lower urogenital tract. Even urination, that one starts almost at birth and periodically continues throughout life, never escapes psychic meddling in a large percentage of individuals. Nor can one say that these individuals are psychoneurotics. If they are, then at least 50 per cent of all males are to be classified thus. For that is about the percentage that finds it impossible, or almost so, to urinate in the physician's presence. Just so soon as he leaves the room and closes the door, the trick is turned. Singularly enough, the older the physician grows the more journeys he must make from the room. Assuredly, there is something in gray hair that starts urination-inhibiting impulses in patients.

Unfortunately our search in psychic fields does not stop with that vast horde of urinary hesitators. It reaches far into functional avenues, it covers a larger part of sensory disturbances than any of us suspect and, when it comes to the matter of sex, it almost occupies the entire picture. Often it must work from gross pathologic and structural change to underlying and causal mental fixations. Even more often our search

carries us from fixed or fleeting sensory symptoms to their causes in the mind, things that may have been the children of fears or merely the discomfort memories of former pains that should have died with the removal of the cause.

For time out of mind we have called the outstanding members of these great groups "urogenital" or "sexual neurotics." Usually we did not pause to consider the reasons why they were as they were. They pursued their seemingly endless journeys from doctor to doctor with scant comfort and usually less relief, many of them still do. During those journeys they met little that had to do with a study of what was happening in the mind but an almost endless train of instrumental procedures that served only to deepen the mental scar that made them medical nomads.

As urology has delved more and more into the diagnostic art it has narrowed greatly the range of the so-called "idiopathic." It has found the reasons for a large number of conditions and has developed treatments appropriate to them. It, however, has missed to a great extent the tricks the mind can do and often does in symptom creation in this portion of the anatomy.

Let us consider first that matter of psychogenic sensory symptoms, mentioning at the beginning a very frequent evidence of the fact that there are such things. The patient, usually a married man, presents himself with the statement that he strayed from conjugal paths, thinks he has contracted gonorrhea and has a burning pain at about  $\frac{1}{2}$  inch from the external urinary meatus. The sensation came immediately after he got the idea of infection and has remained. The doctor takes a smear from his urethral secretion, stains and studies it microscopically in the patient's presence, finds nothing, and insists he has no gonococcal infection. Before the patient leaves the office he remarks in wonderment that the pain has disappeared entirely. And it fails to return unless he again gets the fear he has been infected.

Of course the mind more often generates sensory symptoms in the bladder than in any other portion of the tract, and this fact accounts for a great number of cases in which no local cause can be found. As such sensory discomforts center preponderantly in the trigone they naturally go a step further

and disturb urinary function, with frequency of urination as an outstanding feature. Continued over any great length of time, the not infrequent result is change in structure, as will be seen later.

Our commonest form in this group is born of the fear that the bladder will be injured if it is made to hold a large quantity of urine. Most of these mental fixations formerly were found in youth and early adolescence, but of late years the rather widespread fear of prostatic hypertrophy in the male and bladder malignancy in the female has shifted the statistical balance so that the palm may belong to those beyond middle life. The sequence of events runs about as follows: the fear is born and grows, the mind analyzes urinary function to the extent of becoming bladder conscious, trigonal sensitiveness is the next step, and then a constant and seemingly mysterious frequency of urination sets in. It might be of interest to cite several cases.

R. J., age twenty-four; while attending a party at eighteen years of age, had the desire to urinate but, things not being propitious, he delayed it until about two hours later. He had a little difficulty in starting his urinary stream, which he noticed was quite small after the first portion of urine had been passed and, toward the end of urination, it just flowed out without any projectile force, as it naturally would under the circumstances. Being sure he had injured his bladder, he decided to rest it by not allowing it to fill for a few days. By the end of this time he found he developed a trigonal discomfort when the bladder contained but a small quantity of urine. Within a month he was urinating at about half-hour intervals day and night. His father took him to doctor after doctor and, in the absence of findings satisfying to the medical talent, he finally was said to have diabetes insipidus. He was given various glandular products and denied fluids almost to the point of dehydration.

If the doctors had taken the trouble to measure the amount of urine passed at each urination, as well as his twenty-four-hour output, a little arithmetic would have thrown the question of diabetes insipidus into the discard, also five years of treatment would have been avoided.

A careful study proved that the only things wrong with

the patient were an assortment of mental fixations and a bladder of small capacity simply because it had not been stretched for years. Revealing these fixations to him and self-retraining of the bladder brought surprisingly quick cure.

Mrs. F. K., age forty-seven; complained of "pain coming on five minutes after urination and lasting for hours." She had a normal urine, normal bladder and urethra and no apparent pelvic disorder.

She had a neighbor dying of vesical carcinoma who had the same symptom. Her own pain stopped immediately after she was assured nothing was wrong with her bladder.

J. W., age sixty-eight; had been in bed for two weeks complaining of marked discomfort at the base of the bladder with suprapubic transference and was urinating every few moments. He had a self-made diagnosis of prostatic hypertrophy and had convinced his physician that such was the case. The latter was under the impression that, despite his inability to map out a distended bladder, the frequency was practically the overflow of retention.

Examination and later cystoscopy failed to reveal anything abnormal. Questioning elicited the fact that he had two friends with prostatic hypertrophy and that he knew more about the symptoms than a doctor was likely to know after years of observation of such patients. He was cured within a half hour of the time he was assured that there was no prostatic obstruction and the only reason for his frequency was the fears he had built up.

The question of deranged urinary function, aside from that secondary to trigonal discomfort born of mental concentrations, is an interesting and decidedly important one. Some of these cases may start in infancy as the result of a pinpoint urethral or preputial meatus and continue for life, though the initial obstruction has been removed. Others develop the pernicious urinary habit during youth as the result of ideas, perhaps, in such an experience as outlined in the first case cited. The outcome of both is the habit of making urination a matter of straining to force the urine out rather than one of normal sphincter relaxation. In the mind there is the conviction of obstruction to urination, as a rule. The patient refuses to stand and wait for relaxation, which his mental inhibitions

make more and more difficult, but takes what, to him, is the time-saving method of helping out with his abdominal muscles.

Of all urinary habits this writes the most easily readable of cystoscopic pictures, for the bladders of such patients show all grades of trabeculation. Early the picture is suggestive of *tabes dorsalis* except that there is spasm instead of relaxation of the vesical outlet. After years of the practice the bladder would do justice to a chronic prostatic obstruction, except that there is no obstruction. Nor is there vesical outlet relaxation to suggest *tabes*. Instead of stretching, as one might expect, the bladder grows smaller because of the great hypertrophy of muscle fasciculi and the patient has to arise at night. Owing to this he consults the physician, who naturally assumes from the history of difficult urination, which the patient forgets has been present for years, and the nocturia, that lower tract obstruction is present and some time later he reaches the cystoscopic table.

Some really do develop a prostatic obstruction, get a suprapubic prostatectomy and the wound leaks for weeks or months because they still strain to start the urinary stream. Cure depends upon the removal of the fixation and the correction of the urinary habit.

Then there is that rather large group of patients of uneasy conscience and good sensation memory who persist in having urethral, perineal or rectal pains or discomforts long after the reasons for them have gone. In the distant background is a severe gonococcal infection for the treatment of which much traumatic urethral instrumentation has been carried out. In the ever-present and immediate background is the conviction that something still is wrong. Their idle moments are filled with apprehensions and they find it difficult to get the mind away from the urethra long enough to concentrate on the other needs of life. They think they get temporary benefit from either the passage of a sound or an endoscopic treatment, but before long the symptom returns. The treatments only serve to fix the mental scar.

Finally someone, after a careful study that reveals nothing that locally could serve as a cause, sits down and searches for the mental fixations, opens the patient's eyes to what is going on, gets him to take a two or three months' rest from treatment

and, if the salesmanship is good, produces a cure. Telling any of these patients that it is "all in the head" gets mostly nowhere. They must be shown how and why.

R. S., age thirty-two; had a gonococcal infection with much instrumental treatment twelve years before. He was told he was cured, but because of shreds in his urine he did not believe it. Shortly he developed an uncomfortable sensation along his urethra with an occasional slight twinge of pain. He went to an urologist who impressed him greatly by passing an endoscope and looking for the trouble. Feeling that this gave sensory relief he returned for more treatments and continued to do so for the whole of the intervening time.

A careful study revealed only that the posterior urethral mucosa was quite bluish from the repeated applications of silver nitrate and, because the urologist had not mopped out the overflow silver nitrate solution before withdrawing the endoscope, the bulbar portion of the canal had built up a squamous coating to protect itself.

Further endoscopic treatment was refused and the patient was told what it was all about. The salesmanship was not convincing for he returned to the other urologist for eighteen months more of endoscopic applications. He then returned, agreed to go three months without treatment, kept the promise for a month and then contracted gonorrhea. This did not pass to the posterior urethra, but he knew endoscopic treatments should not be done while he had gonorrhea. When the gonorrhea was gone the urethral discomfort and pains were gone also and they failed to return. At least, we can score one in favor of gonorrhea.

It would be a simple matter to cite a large variety and a large number of cases wherein the erasure of mental fixations, following a most careful urogenital study, were the only means used in the eradication of both sensory and functional symptoms. The danger is that one not skilled in such studies will overlook true causal pathology. One makes no mistake, however, in the presence of minor changes of function or mild sensory symptoms, particularly if the urine is normal, to go rather carefully into what the patient is thinking about his troubles. Usually it is a simple matter to find the true underlying fears and fixations that will explain much that otherwise

seems obscure. Particularly does this apply to the urinary functional disturbances before the age of thirty-five years. In later life there more often is easily demonstrated pathology to explain such dysfunction and it is only after the proof that such pathology does not exist that blame should be shifted to the mental sphere. Of course, this applies to the earlier age groups as well.

When one turns to the various departures from what we have been pleased to call "normal sex function" he finds himself in a psychologic sea. So much of it has to do with what a man thinks that the physician soon finds himself relegating endocrine urge to a comfortable but almost forgotten seat in the back row. If he looks to the mind for the explanation of all of the cases that consult him for impotence and premature ejaculation he will make few, if any, mistakes.

The urethral lesions so commonly said to produce these disquieting experiences are found about ten times as often in the blood brothers of Don Juan than in those who stumble and fall this side of their shrine. But even these soul-sick brothers, who greatly need a friend, must get an urogenital study if one would break the tie that binds the psyche to their fallen hero. Nowhere in the entire realm of psychogenic projections is it more needful that the sorrowing one be immovably convinced that his doctor knows what he is talking about. In no other way can he surely be readjusted to his opportunities.





## CLINIC OF DR. CLIFFORD B. LULL

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### THE DIAGNOSIS AND TREATMENT OF THE ANEMIAS OF PREGNANCY

**Case History.**—The patient presented this morning is suffering from a condition which is a rather infrequent and serious complication of the pregnant state. Her family history is negative. Her personal history is negative except for an attack of rheumatic fever during adolescence. This is her third pregnancy, the last being five years ago, both the earlier ones having been spontaneous and without history of toxemia or complications during pregnancy or the puerperal period. She was referred to the hospital by her family physician with the diagnosis of toxemia of pregnancy, and entered the hospital complaining of swelling of the ankles, dyspnea, palpitation and exhaustion.

**Physical Examination.**—Physical examination on admission shows a very marked pallor to the skin and mucous membranes which she has noted for at least two months. She is thin, pale, anxious, and depressed. The neck veins are prominent and pulsating. The left lobe of the thyroid is slightly enlarged. The lungs are clear. The heart is rapid, the rhythm regular, there is slight enlargement to the left, and there is a suggestion of a blowing murmur over the mitral area. The umbilicus is enlarged to the umbilicus, which would correspond to the cessation of menstruation, is rather soft, and there are no tenderness. The liver cannot be definitely outlined. There is some pitting edema.

**Laboratory Report.** On admission, urine showed a faint trace of albumin with 25 to 50 white blood cells to a high

power field. The hemoglobin was 22 per cent, 1,160,000 red blood cells, 7700 white blood cells; 79 per cent polymorphonuclear leukocytes, 20 per cent lymphocytes, 1 per cent monocytes. There was poikilocytosis and macrocytosis. Reticulocytes, 0.4 per cent. Volume index equals 1; saturation index equals 1.

*Blood Chemistry.*—Serum albumin, 3.58 per cent, serum globulin, 1.94 per cent, blood urea nitrogen, 11.2. Takata-Ara test negative. Blood Wassermann negative. Gastric analysis shows almost absence of free hydrochloric and positive benzidine reaction. Microscopic gastric analysis shows many white blood cells, and few epithelial cells. Electrocardiogram shows evidence of some myocardial damage.

*Progress.*—This patient has been under observation for a period of eight weeks, during which time there has been a definite improvement in her general condition, and the blood count has shown steady improvement, so that at the present time the hemoglobin is 51.2 per cent, 2,760,000 red blood cells. Of 1000 cells counted, there were no reticulocytes seen. The pulse and temperature, which were elevated on admission, have subsided to about average.

*Treatment.*—On admission this patient was given the usual routine care, plus the administration of feosol, 6 grains t. i. d., and 1 ampule of Lilly's extract of fresh liver, t. i. d. After observation for several days, with no signs of improvement, it was thought advisable, after consultation with the medical department, to give repeated small blood transfusions. Eight of these transfusions were given in conjunction with the iron and liver medication, during which time some definite improvement was shown. Inasmuch as the question arose as to the advisability of an interruption of the pregnancy, treatment was discontinued for a week. During this time there was a marked reduction in both hemoglobin and red cells, with an increase in reticulocytes. Transfusions were again resorted to, and steady improvement has followed.

*Diagnosis.*—This patient has a severe anemia of pregnancy bordering on the pernicious type.

*Prognosis.*—The prognosis, as far as the patient is concerned, is favorable. The prognosis, as far as the continuation of the pregnancy is concerned, is unfavorable. In all

probability this patient cannot be carried through to full term, and if the uterus is emptied, either spontaneously or by intervention, she should show continued improvement as far as her anemia is concerned.

**General Discussion.**—During the past few years the question of the various anemias that occur during the pregnant state have been repeatedly brought to our attention. The simplest classification of this condition is probably: (1) simple anemia, (2) severe anemia, and (3) severe anemia of the pernicious type.

**Simple Anemia.**—Many observers believe that all women have a moderate anemia during pregnancy which is possibly physiologic. This is a mooted question, however, as the chances are most people at some time of the year have a reduction in both hemoglobin and red cells. It has been repeatedly stated that the simple anemia is the result of increased blood volume. The most important cause, however, is probably insufficient diet. Second to this are gastro-intestinal disturbances that occur during pregnancy, particularly if there is a reduction of free hydrochloric acid and total acid in the gastric secretion. The occurrence of any of the acute infections, as la grippe, pyelitis, and other intercurrent infections, will almost invariably cause an anemia which is already established to become worse during pregnancy. Many of these simple anemias are unrecognized, particularly if the hemoglobin is not reduced below 75 per cent and the red cells not below 3,000,000. As a rule, these patients do not complain of unusual symptoms, and unless one routinely observes the blood count they are oftentimes unrecognized. Occasionally the patient will complain of some lassitude, slight dyspnea, and some pretibial edema. This is particularly true in a patient who already has a slight anemia, who becomes pregnant, and who during her pregnancy suffers from some acute mild infection. The treatment of simple anemia consists first in diet. For many years it has been the custom of many obstetricians to reduce very markedly the protein intake during pregnancy. This is true if the patient shows any slight evidence of toxemia. There are very few cases of kidney involvement during pregnancy who require a nonprotein diet, and if the patient is normal, she should have an adequate amount of protein

during the entire pregnancy. The pregnant woman should have a reasonable amount of protein per kilo of body weight for the development of energy and the stimulation of cellular activity and metabolism. It seems, therefore, that a suitable diet for the average pregnant woman is one that contains moderate protein and is high in vitamin and low in fat. In addition to proper diet, sunlight, if necessary by the ultra-violet rays, is of benefit. Medicinally, the use of iron is probably all that is necessary in this type of anemia, either in the form of Bland's mass or reduced iron. The dose should be rather large, either 60 to 100 grains iron ammonium citrate daily, or 30 to 60 grains of reduced iron daily. In some cases where there is a marked decrease in the hydrochloric acid of the gastric secretion, 15 minims of dilute hydrochloric acid given three times a day, in addition, is of benefit. The use of iron, hypodermically, which was so commonly resorted to in the past, should never be resorted to unless it is impossible for the individual to take iron by mouth. Copper, liver extract and ventriculin have been used with satisfactory results.

**Severe Anemia.**—When the hemoglobin is 45 per cent or less, and the red cells below 3,500,000, the patient is usually suffering from that type of anemia which, according to this classification, would be noted as severe. Most of these cases originated as simple anemias unrecognized until either definite symptoms arose or a study of the blood revealed the true condition present. It is of importance to study the blood of women in pregnancy because, if a slight anemia is found, adequate treatment will prevent its progress to the more severe type. If a reduction of hemoglobin and red cells has been found at any time during the pregnancy, frequent blood counts should be taken to make sure that the blood is maintained at an adequate level during the entire pregnancy. The treatment of the severe type of anemia seen in pregnancy is as discussed previously under the treatment of simple anemia, plus the giving of small blood transfusions. There has been much discussion as to the advisability of transfusions, but if used intelligently, they are of unquestionable therapeutic value. Small transfusions given every two or three days are much more efficacious than massive transfusions, and result in fewer

unfavorable reactions. The usual safeguards as stressed in the giving of any blood transfusion should surround the patient at this time.

**Severe Anemia (Pernicious Type).—**This type of anemia, which is very frequently fatal, fortunately is rather rare. Some authorities estimate the mortality rate as from 60 to 70 per cent. There are many of these that probably are not diagnosed, but are put down as being cardiorenal-vascular disease. There is in this type of anemia a very marked deficiency or total absence of free hydrochloric acid and also a lack of the intrinsic factor of Castle in the gastric secretion. This lack or loss of intrinsic factor, however, is only temporary, while in the addisonian anemia it is permanent. Cord changes are seldom present. The diagnosis is made from a careful study of the blood. The red cells are more greatly reduced than the hemoglobin. The white cells vary, but usually a normal or slightly increased white count is found. The red cells are larger than normal. The volume index is usually greater than 1. The fragility of the red blood cells is normal or reduced. The bleeding time and clotting time are variable. The iron index is normal or greater than normal. The treatment must be active and intelligently administered. Although blood transfusions probably are not used frequently in the very critical patient, a few small blood transfusions will improve the patient, while the administration of liver extract or hog's stomach or autolyzed yeast is given a chance to become effective. The liver extract of either Lilly, Mulford or Valentine's E29 will be found to be efficacious. A careful check of the reticulocyte count should be made at regular intervals of from three to five days. A diet similar to the diet used in the simple and severe anemias of pregnancy is indicated. It is particularly essential that the treatment be continued until the blood count is normal, and even after delivery careful observation should be made to see that no relapse occurs.

**Other Anemias.—**The presentation of this patient has brought up the discussion of the foregoing types of anemia, but your attention is called to the secondary anemias following the various hemorrhages of pregnancy, and the anemias, hemolytic in type, which are a result of postpartum sepsis. In these conditions, frequent small blood transfusions are of

the utmost value. There is reported in the literature an occasional case of splenic anemia, aplastic anemia, and various other blood dyscrasias, which, as in cases other than those in the pregnant, are very frequently fatal. These, fortunately, are not frequent.

The question always arises in a patient who is suffering from a marked anemia, as to whether or not the pregnancy should be interfered with. This is very seldom necessary as the simple and severe types of anemia usually respond to treatment very satisfactorily, and the severe anemia of the pernicious type will usually abort spontaneously. This has been my experience in the few cases that I have seen of this severe or pernicious type of anemia complicating pregnancy. Any patient who suffers from an anemia of any degree during her antenatal period, should be particularly safeguarded against blood loss during delivery or postpartum. These patients also are more liable to infection, and their convalescence, if they have an exhaustive labor, is usually prolonged.

**Summary.**—It is of utmost importance that the blood of the pregnant woman be observed from time to time. An unrecognized or inadequately treated anemia of pregnancy probably plays an important part in the development of many of the complications of pregnancy, labor, and parturition, such as premature birth, dental caries, faulty lactation, delayed involution, postpartum psychosis, and because of lowered resistance, the occurrence of infections such as tuberculosis. The recognition of anemia during pregnancy with adequate treatment is unquestionably a factor in the decrease of maternal mortality. Too much stress cannot be laid upon this element of antenatal care. Even though we have today, in our armamentarium, many methods of combating anemia, it is probably one of the most frequently overlooked complications of pregnancy and parturition, and if the presence of the disease is unrecognized, these valuable adjuncts of medical treatment are of no avail. If anemia is discovered, adequate treatment should be instituted at once, and the patient should be observed most carefully during the entire pregnancy, in order to keep the blood count at a proper level.

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## CLINIC OF DR. BURGESS GORDON

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### THE INDICATIONS FOR AND THE TECHNIC OF ARTIFICIAL PNEUMOTHORAX

THE idea of employing artificial pneumothorax for the treatment of pulmonary tuberculosis was conceived with the sound principle that immobilization is valuable for the control of inflammation in any part of the body. The history of its use, according to Myers,<sup>1</sup> dates back to the fourth century when Greek physicians introduced air into the chest for the treatment of disease. James Carson, a Scotch physician practicing in Liverpool, was apparently the first to conduct experiments on animals and he collapsed a lung successfully in 1888 by introducing air into the pleural cavity. His experimental studies were significant because Itard, Selle, and others had observed that patients could breathe satisfactorily and survive with spontaneous pneumothorax. Although Carson recommended artificial pneumothorax for the treatment of pulmonary tuberculosis he did not use it on patients and thus his writings received little attention clinically. Carl Forlanini of Italy recognized the possibilities of collapse therapy and in 1888 performed the first artificial pneumothorax on a patient with pleural effusion and four years later he actually collapsed a diseased lung. Murphy of Chicago used the method successfully in 1898 and is credited, with Forlanini, as having established the clinical value of pneumothorax. Samuel Robinson of Boston, according to Stoll,<sup>2</sup> was the first to employ pneumothorax treatments in the eastern part of the United States and devised an apparatus for the purpose; his first case was a patient of Dr. Joseph Pratt. Brauer, McRuer, Tice and Lumke are other names connected with the early work of artificial pneumothorax.

From the earliest times the suggestion of new methods of treatment has been followed almost always by waves of criticism, skepticism and enthusiasm. Artificial pneumothorax, no exception, has been alternately condemned and supported, even by the most celebrated workers in tuberculosis. The reason for this is traceable, no doubt, either to the observer's good fortune or misfortune to witness a group of striking recoveries or a series of catastrophes; impression rather than experience has also played a part. As a result, there has been a tremendous volume of contradictory literature. It is evident in some publications that the unfavorable results were due to the improper selection of cases, and conversely that the favorable results in other cases would have occurred in the ordinary course of healing. Thus, one gains from the literature that collapse therapy in tuberculosis requires a certain knowledge of the physiopathology of the disease.

#### PHYSIOLOGIC CONSIDERATIONS

Since rest is an important measure in the treatment of pulmonary tuberculosis there is a tendency to ascribe the beneficial results of artificial pneumothorax to the degree of immobility of the affected lung. However, experience indicates that the degree of collapse is not necessarily an indication of the degree of healing that may occur. It has been noted, for example, that a moderately collapsed and functioning lung sometimes shows greater improvement than an extremely collapsed and nonfunctioning lung. The results are no doubt influenced by the type of infection and the individual's natural resistance, and also related to the degree of contractility and expansibility of the lung, the drainage of suppurative areas, inflammatory processes located near the base of tugging adhesions, cavity formation, shifting of the mediastinum, and the traumatizing effect of cough.

Under normal conditions the lungs completely fill the pleural spaces and thus the pleural surfaces are actually only potential cavities. The pleural spaces contain serous fluid, a strong adhesive force which causes the lungs to be retained against the chest wall. Since the lungs contain a considerable amount of elastic tissue they exert a constant pull away from the chest wall. Due to the adhesive effect of the serum upon

the pleural surfaces and the normal contractility of the lung, a negative intrapleural pressure is created. The pressure is approximately 9 mm. of mercury at the end of inspiration and about 7.5 mm. at the end of expiration; there is a considerable variation in different individuals. Thus, it becomes evident that there is a difference physiologically between collapse and compression of the lung in artificial pneumothorax. Collapse is actually a relaxation of the lung due to a comparatively small amount of air having been introduced into the pleural space; the separation of the pleural surfaces definitely interferes with the adhesive action of the serous fluid and permits the lung to contract. Compression signifies that a definite force has been exerted upon the lung by a relatively large amount of air introduced into the pleural cavity. This causes a marked reduction in the negative pressure, a tendency to develop a positive pressure. Thus, the lung is no longer able to expand freely; eventually it becomes compressed.

The significance of the various changes in intrapleural pressure is illustrated further in studying the effects on the mediastinum. In normal individuals the mediastinum is so mobile as to be easily shifted from its medial position to one side or the other. With small changes in the pleural pressure on one side of the thoracic cavity there is little or no influence upon the mediastinum or on the opposite lung. However, the introduction of a large quantity of air under high pressure into one pleural cavity will not only compress the lung on this treated side but will also influence the lung on the opposite side due to displacement of the mediastinum. This results in lowered vital capacity, causing dyspnea; and in some cases there are signs of a disturbed pulmonary circulation. With a fixed mediastinum the problem is different and larger quantities of air may be introduced without influencing the opposite lung. However, the desirability of this measure upon the diseased lung is open to question, since tuberculous tissue, as with other inflamed tissue, is easily damaged by pressure and distortion. This is illustrated in the progression of processes at the base of adhesions, the changes being related to the "tugging" movements during expiration. Thus, while the high intrapleural pressure compresses the lung generally the adhesion causes it to remain expanded at one point. It appears further

that cough is more apt to disturb the compressed and more or less immobilized lung than the contracted or relaxed lung, possibly due to differences in buoyancy. In regarding the problem physiologically it seems that the ideal amount of air for introduction into the pleural cavity is that which is sufficient only to cause relaxation, resulting in a moderate collapse of the affected lung.

So-called "bilateral pneumothorax" is physiologically sound in selected cases providing a negative pressure is preserved at least on one side. The reason for this provision is explained by Graham<sup>3</sup> who points out that the passage of air down the trachea and into the lungs is essentially a suction process and is therefore dependent upon the existence of a negative intrapleural pressure at some time during the action of inspiration.

#### SELECTIVE PNEUMOTHORAX

A physiologic phenomenon which is closely related to the pathology of pulmonary tuberculosis is so-called "selective pneumothorax." It appears, according to Myers,<sup>1</sup> that diseased areas, with the exception of consolidations and dense fibrosis, collapse more readily than normal areas owing to the fact that in such areas there is little or no diminution of contractility but rather a marked impairment of expansibility. This favors the mechanism of selective collapse which is essentially a collapse of the diseased part of the treated lung and a more or less normal function of the unaffected part. According to Cutler,<sup>4</sup> the mechanics of selective collapse are attributed to the inability of tuberculous tissue to resist the pressure of the pneumothorax and, thus, with each inspiration the expansion of the part becomes less and less. Conversely, the normal part of the treated lung which has retained its normal elasticity will resist the pressure of the pneumothorax. Due to the expansile action of the normal part air in the pleural cavity will be forced toward the diseased area. Thus, the diseased area gradually yields and becomes collapsed. Ehrenberg,<sup>5</sup> differing with this general view, regards Archimedes' *Principle of Buoyancy* as the cause of selective collapse. This implies that the air within the lung is of higher density than the air within the pleural cavity, and thus a buoyant force will be transmitted through the alveoli by the air in the air passages upon the gas

in the pleural cavity. As a consequence, the air in the pleural cavity will be forced upward and its bulk will accumulate over the apex of the lung. Thus, the upper lobe, due to gravity and the pressure of the insufflated air, will not only be separated from the chest wall but may even drop to the first or second interspace. According to Ehrenberg the satisfactory results of such a collapse are due to the fortunate location of the lesion at the point where the gas accumulates.

#### PATHOLOGIC CONSIDERATIONS

Numerous observations indicate that no serious harm occurs in the normal lung which is maintained in a collapsed state over a long period of time. The chief alterations are the development of fibrous tissue in the pleura and variations in the blood vessels. The degree of permanent change appears to be somewhat dependent upon the underlying pathology.

According to Charr<sup>6</sup> there is a decrease in the number and caliber of the pulmonary blood vessels. The finer ramifications begin to disappear while the larger vessels become short and narrow, within about two months after collapse is instituted; there is marked thickening of the adventitia with proliferative endarteritis. The changes tend to become permanent if the collapse is maintained for one year or more.

The bronchi and bronchioles show atrophy and sclerosis. Infiltrating into the collapsed lung are fibrous strands which originate in the adventitia of the blood vessels, the connective tissue of the interlobular septa and the pleura. Pleural exudate augments fibrous tissue formation, which later invades the parenchyma whether it is normal or diseased. Graham<sup>7</sup> suggests that pneumothorax incites proliferation of fibrous tissue at least in the pleura. In the lung that has been allowed to reexpand there are fibrous adhesions between it and the chest wall and not infrequently there is obliteration of the pleural space.

There are differences in the closure of cavities. Charr<sup>6</sup> rarely found a complete flattening or proximation of cavity walls, even in those cases where collapse had been satisfactory and the disease stabilized. Three cases that had been followed by the x-rays showed a gradual enlargement of the cavity in the atelectatic lung; postmortem suggested this was due to

the retention of necrotic matter. A few were obliterated or transformed into scar tissue, the result apparently of relaxation of the tissue surrounding the cavity wall. Evidently the closure and healing of cavities depend upon satisfactory drainage, the absence of check valves which would favor the retention of air and dilatation of the cavity, as well as upon any relaxing or forceful action of artificial pneumothorax.

#### INDICATIONS FOR ARTIFICIAL PNEUMOTHORAX

In considering the indications it is important to realize that tuberculosis is a variable and treacherous disease. It is characterized by periods of exacerbation and improvement that are sometimes difficult to explain on the basis of the extent and degree of infection. Patients may improve without apparent cause or there may be a retrogression even when the most careful methods are employed. In some instances experienced workers in tuberculosis cannot predict the outcome. Thus, a good deal of judgment is required in the selection of cases for collapse therapy as well as in their successful conduct over a long period of time. The well-established hygienic-dietetic-rest regimen should be tried in almost all cases before instituting pneumothorax. Enthusiasm for artificial pneumothorax should be carefully checked in cases that are progressing satisfactorily. The procedure is not entirely without danger of complications, and furthermore it must be continued indefinitely. Since it is essentially a supplementary measure to the general regimen there should be no false encouragement as to its replacing any fundamental treatment.

The indications for unilateral artificial pneumothorax are as follows:

1. The most obvious need for collapse therapy is in those patients with active progressive disease of one lung which is not responding to a carefully regulated hygienic-dietetic-rest regimen. In such cases there is danger that the infection will spread to the opposite lung and to the unaffected part of the diseased lung.

2. In patients with a lesion that has become stationary. The need for collapse is less urgent but the instability of the temperature and pulse rate with other evidences of toxemia emphasize the potential danger of the disease.

3. In complications, such as diabetes, tuberculous laryngitis, and recurring or severe hemoptysis, the latter being limited to cases in which the site of bleeding is quite definitely established.

4. In cases of advanced or bilateral disease with approximately one third of normal pulmonary tissues remaining, but without evidence of emphysema; the general condition should be reasonably good in spite of any toxemia.

5. To control the persistent formation of fluid in pleurisy with effusion.

6. To maintain a collapse of the lung in spontaneous pneumothorax which is due to tuberculosis.

7. In all unilateral cases first diagnosed during or immediately following pregnancy.

8. In patients with "open" tuberculosis who are uncooperative at home and cannot be treated in sanatoria.

The indications for simultaneous bilateral artificial pneumothorax are:

1. In cases with reactivation or extension of the infection in the relatively good lung, and in processes that are essentially equal in both lungs; the cases should be of the ulcerative type with cavitation.

2. To control toxemia after the original pneumothorax has been established.

3. In cases with displacement of the mediastinum and in recurring hemoptysis of the hitherto untreated lung.

An important point in the selection of cases for unilateral artificial pneumothorax is the consideration of contralateral disease, *i. e.*, the possibility of stirring up trouble in the relatively sound lung, either because of extra work thrown upon it or because of displacement phenomena of the mediastinum. Sometimes the exact effect can be determined only by a therapeutic test. As Matson, Matson and Bisailon<sup>8</sup> have pointed out the various types of contralateral lung processes vary greatly in their prognostic significance. In general the lung to be treated should be considered as to its degree of activity rather than the extent of involvement; the lesion in the opposite lung should be regarded as possibly related to the more active and extensive process in the lung to be treated. The importance of considering the degree of activity as more important than the extent of the lesion, *per se*, is emphasized in the

marked reduction of toxemia and pulmonary symptoms that sometimes occurs in patients who would be given up as hopeless if judged entirely on an anatomic basis. A bilateral case may be selected for collapse of one lung if this markedly diseased lung presents evidence of chronic change and the opposite lung shows comparatively less disease or a slowly progressive infection. This dictum should at least be considered correct until proved otherwise.

The use of simultaneous bilateral pneumothorax in advanced cases with cavitation has an increasing number of advocates and the results have justified the treatment. Strict bed rest is essential in almost all instances.

Phrenic paralysis in combination with artificial pneumothorax may be employed in bilateral cases with advanced fibrotic lesions on one side and earlier and rapidly advancing lesions on the other; the pneumothorax is used to collapse the less affected lung, the paralysis being utilized on the opposite side.

In the selection of cases according to sex there is no need to differentiate; the sexes react essentially the same. There is an increasing tendency to treat children with the adult type of tuberculosis according to the indications for adults. Gross and English<sup>9</sup> find that juvenile patients who harbor the adult form of tuberculosis do poorly under the usual hygienic-dietetic-rest regimen. They strongly advocate the use of artificial pneumothorax. It should be emphasized that collapse therapy is not indicated in the childhood type of tuberculosis. It may be used in patients up to sixty years of age.

### CONTRAINDICATIONS

The contraindications are: cardiac failure, emphysema, asthma, renal disease, and gastro-intestinal tuberculosis. The danger of inducing artificial pneumothorax in emphysema cases should be stressed. Such patients are greatly disturbed; the procedure may prove fatal. It is important to emphasize also that the degree of emphysema may be underestimated, also that the underlying tuberculous infection may be masked. A flattened diaphragm with increased illumination of the lung fields in the x-rays are warning signs of emphysema.



## DESCRIPTION OF PNEUMOTHORAX APPARATUS

Practically all pneumothorax apparatus may be classified according to the principle involved as follows: the gravity principle, gasometer principle and aneroid-recording principle.

In the gravity type, of which the Samuel Robinson apparatus is an example, there are two bottles, one of which introduces air into the pleural space as the water from one bottle passes into the other, according to the physics of displacement.

The gasometer type, of which the Bethune apparatus is an example, consists of two cylinders constructed as a telescopic couple; the air passes through a connecting tube as the inner cylinder descends.

The aneroid-recording type<sup>10</sup> consists of an aneroid chamber, the movements of which, in response to the changes in intrapleural pressure are recorded on a chart moved by means of a kymograph.

Apparatus consisting of one or more syringes should not be used if their principle depends upon forceful pressure.

Filtered atmospheric air is now commonly used in all introductions. The pneumothorax needle should be a No. 19, 3½ inches in length, a small curved bevel, with a convenient nipple for connecting with a syringe or rubber tubing. There are special needles providing cut-off valves with or without side openings at the tips, as for example, Loving's needle, the Saugman and the Floyd needles.

## THE TECHNIC FOR INTRODUCING THE THORACENTESIS NEEDLE

The technic for introducing the needle requires experience, judgment and care; certain steps should be routine. Before introducing the needle the patient should be fluoroscoped in the upright position, then placed on an operating table with his affected side elevated and supported by a pillow. The fifth or seventh interspace in the midaxillary line or slightly posteriorly is selected and the site painted with a tincture of iodine and washed with alcohol. A small sterile sheet with an opening about 4 inches in width and 8 inches long is placed over the chest in such a manner as to expose the site of operation. An injection of 0.5 per cent novocain is made under the skin until a wheal is produced: then a small incision about 1 mm. in length is made with a pointed scalpel and a number 22 needle

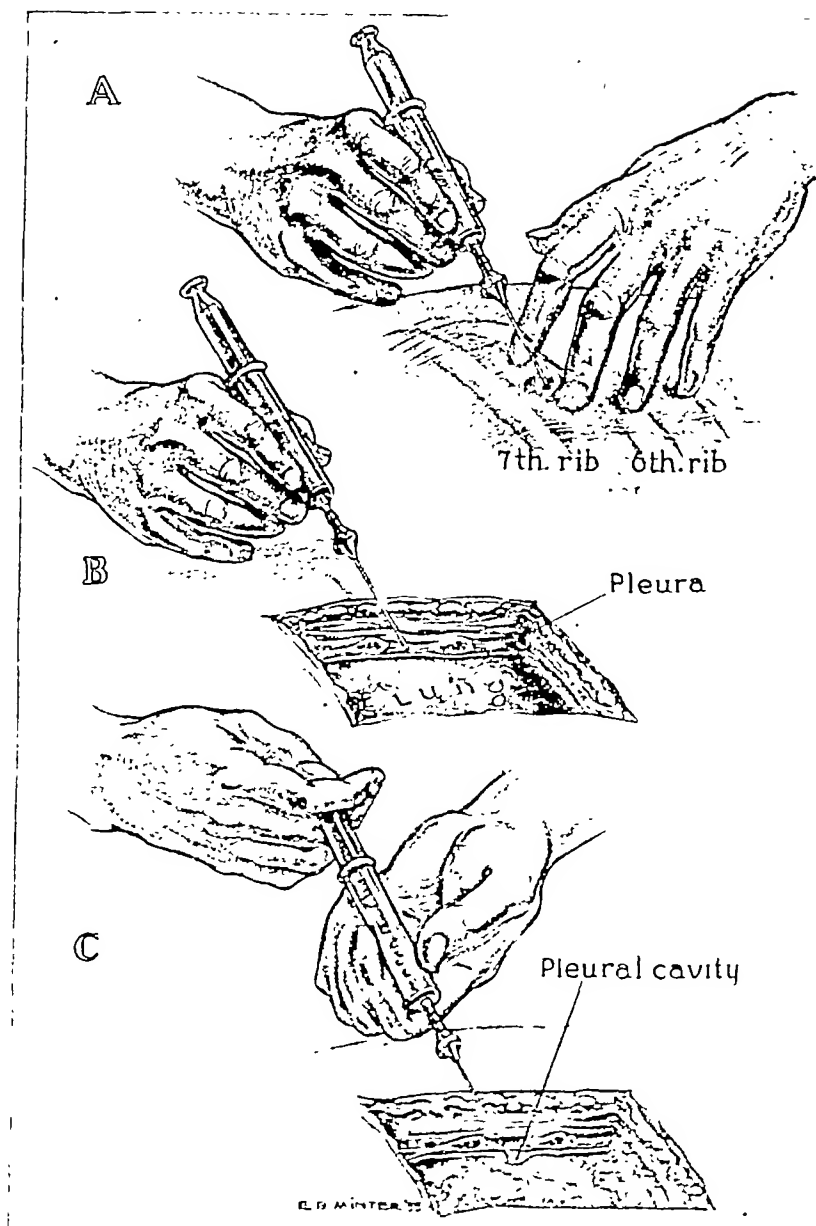


Fig. 64—The technic of anesthesia and the introduction of the needle in an initial artificial pneumothorax. (Collected papers dedicated to Henry A. Christian; B. Gordon.)

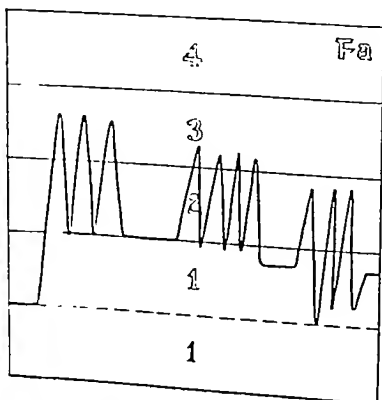
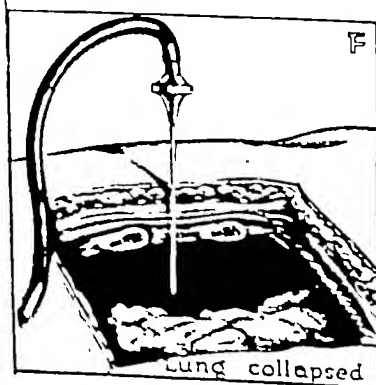
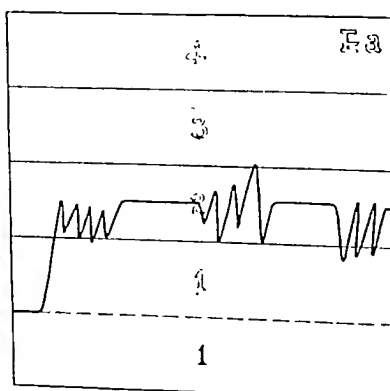
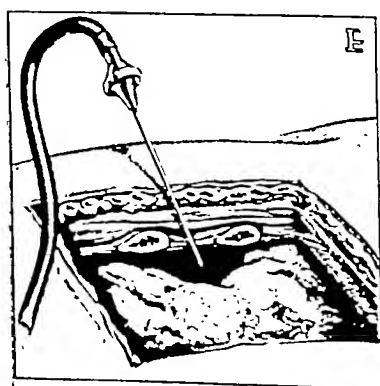
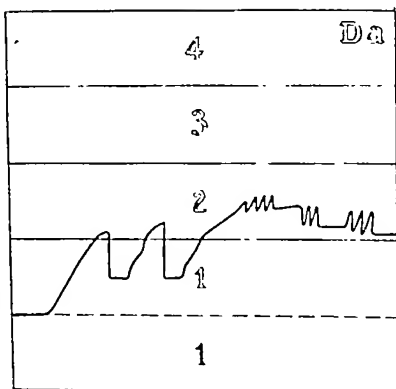
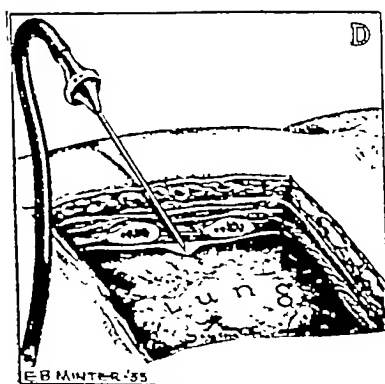


FIG. 15.—The collapse of the lung, and the corresponding intrapleural pressures in progressive artificial pneumothorax, as traced with the recording apparatus. (Collected papers dedicated to Henry A. Christian; B. Gordon.)

is introduced to carry the anesthesia into the deep tissues of the chest as far as the pleura (Fig. 64, *A*). These procedures, except for the initial hypodermic injection of the skin, should be entirely free from pain. After the local anesthesia has been obtained the pneumothorax needle attached to a syringe containing salt solution is slowly and carefully introduced at an angle of about 85 degrees (Fig. 64, *B*). At intervals the plunger of the syringe is carefully withdrawn in order to obtain any evidence that the needle has entered a blood vessel (Fig. 64, *B*). As the needle reaches the parietal pleura there will be a sense of resistance which is lost as it passes into the pleural space; in some instances the point will be felt "scratching" against the lung (Fig. 64, *C*). The syringe is then detached to allow air to enter the pleural space which may occur as a result of the negative pressure; then the syringe is reattached and the plunger "pulled." If bubbles rise in the column of fluid it is certain the needle is in the pleural space (Fig. 64, *C*). The needle is then ready for connection with the pneumothorax apparatus (Fig. 65).

#### THE USE OF THE APPARATUS

**The Initial Pneumothorax.**—In using Samuel Robinson's apparatus (Fig. 66), bottle "B" is elevated, valve "P" turned parallel (open) with the wood back, and valve "M" moved to the vertical position (closed); valves "K" and "L" are then opened (horizontal and vertical positions respectively) in order to bring the manometer and the pleural cavity into communication; with these positions the bottle system is completely shut off.

With the pneumothorax needle in the pleural cavity and connected with nipple "H" of the apparatus the water column will rise in the manometer and show oscillations of negative pressure. This indicates a free pleural space and air may be introduced with safety. Under no circumstances should air be given if there are slight negative and positive oscillations or no greatly sustained negative pressure as such readings suggest that the needle is in the pulmonary tissue. To introduce air, valve "K" is moved to the vertical position (closed) and valve "M" turned to the horizontal plane (opened). This shuts off the manometer and brings the pleural cavity into communica-

tion with the air in bottle "A." The water column in bottle "B" will gradually descend as it enters bottle "A," thus displacing air from bottle "A" into the pleural cavity. The rate of flow is governed by the height of bottle "B." Valve "K" may be kept open during the entire treatment so as to obtain oscillations in the manometer.

After introducing 25 cc. of air, valve "M" should be closed and valve "K" opened. This stops the flow of air and the manometer will record the intrapleural pressure. After noting the oscillations and if the intrapleural pressure is still negative a further small introduction of air should be given as previously. These steps are repeated until the patient has received

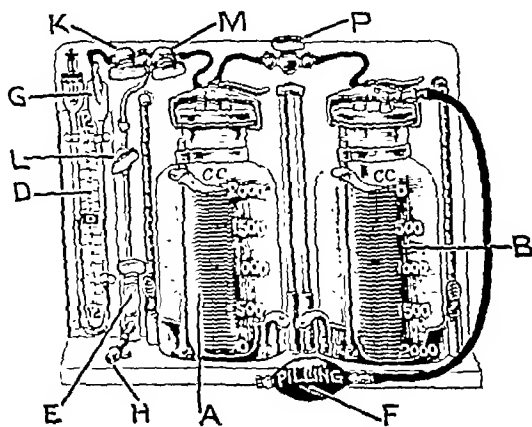


Fig. 66.—Samuel Robinson's artificial pneumothorax apparatus.

between 100 and 200 cc. of air. The treatment should be stopped at any time if the patient complains of pain or shortness of breath, regardless of the pressure and how much air has been introduced. In cases showing tension pneumothorax due to an excessive introduction, some of the air should be removed with a special syringe;<sup>11</sup> it is inadvisable to use the pneumothorax apparatus for this purpose.

Following the initial pneumothorax treatment it is important to examine the patient fluoroscopically and preferably in the same position as was used for the introduction of air. With the horizontal examination the pneumothorax cavity will be clearly visualized, then if the patient is placed in the upright position, the air will shift to a localized position in the

upper part of the chest. Thus, it is possible to exclude the presence of adhesions; if adhesions are present, the air will remain in the original pneumothorax pocket. This study is also valuable for determining any possible displacement of the heart and mediastinum.

**Refills.**—After the pleural surfaces are definitely separated, all subsequent introductions of air are known as “refills.” If Samuel Robinson’s apparatus is to be used it is set up as previously and the readings are taken after each introduction of 50 or 100 cc. After bottle “B” has been emptied, bottle “A” should be raised and bottle “B” lowered so that the water will be siphoned into bottle “B”; the passage may be started by connecting bulb “F” to nipple “H” and giving one or two compressions; then bottle “B” is raised and bottle “A” lowered, which makes the apparatus ready for use. The treatment is stopped when the pressure becomes approximately minus 2 or neutral or up to plus 2; experience shows that comparatively few patients do well if high pressures are used. If the pneumothorax pressure is excessive, some of the air should be removed; a special syringe<sup>11</sup> or a decompressor<sup>12</sup> may be convenient.

A selective pneumothorax will be obtained most frequently if small introductions are given every three or four days at first, then increasing the intervals to one week, and gradually to ten days or longer. All patients should be fluoroscoped before treatment. In bilateral pneumothorax cases the air may be introduced into each pleural cavity on the same day or alternated. If a positive pressure is used on one side, the other should be definitely negative. Every attempt should be made to maintain a normal position of the mediastinum.

#### DANGER SIGNALS IN ARTIFICIAL PNEUMOTHORAX THERAPY

MacKay<sup>13</sup> has described the immediate dangers to the patient during the administration of artificial pneumothorax, stating that while the accidents are probably unavoidable they are frequently serious and sometimes fatal. Of these the most serious is air embolism, due to the introduction of air into a pulmonary vein. It is suggested by a lapse of consciousness, signs of shock and of cerebral involvement. Sudden severe pain in the chest with dyspnea is a strong indication of spon-

taneous pneumothorax, the result of an injury to the lung. Pleural shock is apparently less common; it may be related to a vagovagal reflex. Cocke<sup>14</sup> believes that a progressive fall in blood pressure and pulse rate, with gradual loss of consciousness, flaccidity, a disturbance of reflexes, sweating, slight clonic movements of the face, upper limbs and trunk, are suggestive. Pleural effusions may occur as delayed reactions and are often attributed to high intrapleural pressures. The complications of bilateral pneumothorax are essentially the same as in the unilateral type except that spontaneous pneumothorax is apt to be more common; laughing and loud talking place undue strain on the lungs and are factors in some instances.

#### THE MANAGEMENT OF ARTIFICIAL PNEUMOTHORAX CASES

Regardless of the striking results in artificial pneumothorax cases the usual hygienic-dietetic-rest regimen should be continued. Appearances and symptoms may be confusing, especially when the physical signs are absent as in a well-collapsed lung. It is perhaps a safe rule that the patient without toxic manifestations may sit in a chair two months after a satisfactory collapse has been obtained and begin to walk slowly for short periods six months later. The blood sedimentation test is considered to be an index of the activity of the lesion and should be used in all doubtful cases. The intervals between treatments and the amount of air to be introduced depend upon the degree and type of collapse, and the general effects. It is an ideal plan to strive for a selective collapse.

In patients who fail to improve with collapse therapy two causes should be considered: (1) Is the affected lung being properly collapsed? (2) Is there a spread to the opposite lung? With an unsuitable collapse pneumolysis may be advisable. This operation requires special training and cases should be referred to a competent surgeon. Some cases will eventually require thoracoplasty. Processes that develop in the opposite lung, despite a satisfactory collapse of the originally treated lung, should be considered for phrenic paralysis or artificial pneumothorax. Oleothorax may be of value in preventing expansion of the lung due to the development of adhesions.

In basal pulmonary tuberculosis with an unsatisfactory col-

lapse of the affected area the use of abdominal compression<sup>15</sup> or phrenic paralysis as a supplementary measure may be valuable.<sup>16</sup>

#### INDICATIONS FOR TERMINATING ARTIFICIAL PNEUMOTHORAX

Artificial pneumothorax should be discontinued because: (1) of a complication on the affected side, as for example, recurring spontaneous pneumothorax or pleural effusion; (2) a spread of the disease to the opposite lung in which collapse measures are inadvisable; and (3) uncontrolled infection of the affected lung. Some cases terminate themselves due to the formation of adhesions in spite of the most exacting artificial pneumothorax treatments.

The voluntary reexpansion of the lung should be considered as follows: (1) minimal cases treated successfully for two years; (2) moderately advanced cases without marked cavitation after four years' treatment; (3) far-advanced cases with cavity formation, after five to seven years. All reexpanding cases should be followed closely with physical examinations and the x-rays. If there is any question of activation the pneumothorax should be reinstituted. It is usually advisable in long-treated cases to consider thoracoplasty, rather than to resort to further pneumothorax.

In evaluating the results of artificial pneumothorax it becomes evident that the proper selection of cases, knowledge of the mechanics of respiration, and a carefully regulated medical regimen play an important part in the results. Artificial pneumothorax is not a procedure for haphazard use; it has limitations and is not without danger. It should not be considered in any sense as a substitute for general measures; there is far more involved than simply the introduction of air into the pleural cavity.

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### DIAGNOSIS AND TREATMENT OF HYSTERICAL APHONIA AND THE DIAGNOSIS OF MALINGERING IN THESE CASES

HYSTERICAL aponia is one of the most common forms of psychogenic paralysis. In order to understand the term it is first necessary to define these words. By hysteria is meant a condition characterized by changes in mood or affect, with alterations in character or personality and with physical or somatic manifestations. Every case of hysteria usually has all of the above characteristics, although one of them predominates and gives the characteristic coloring to the clinical picture. In aponia of hysterical nature, it is the difficulty in talking which overshadows the clinical picture, although the other manifestations are also present to a lesser degree. The term "aphonia" signifies an "absence of voice." This term is not entirely correct in the designation used because, as a matter of fact, there is usually a hoarseness or whispering type of speech rather than a complete absence of all vocal manifestations. When even the whispered voice is absent the term "absitheria," which has been coined by Dr. Chevalier Jackson, is applied.

To understand the mechanism of the problem we must give a brief résumé of the present-day conception of hysteria. Hysteria is regarded as a "flight into disease." It is usually an ineffectual but a determined effort on the part of the patient to escape from reality. It represents the best solution for adjustment that he can make. Usually the effort is poorly carried out and the plan is frequently infantile, and is often an impossible one, but it is a purposive effort notwithstanding.

The physical manifestations are the result of repression in the unconscious of unpleasant experiences which are prevented from reaching consciousness because of their painful associations. Every hysterical symptom has a definite meaning and no therapy can be successful without recognizing this basic fact. It is true that the symptoms may defy direct interpretation but usually the significance and the psychogenic origin can be detected by "probing" beneath the surface. It may require hours of work with the patient before the interpretation of the condition is correctly made.

If the above tenets are correct, then an aphonia of hysterical origin must have as its basis an unconscious or uncontrollable desire on the part of the patient to prevent audible speech. The reason for this is not identical in every case, as will be illustrated.

#### REPORT OF CASES

**Case I.**—An insight into the mechanism of hysterical aphonia is afforded by a woman of forty-five, who was studied many years ago at one of the local hospitals. Her chief complaint was an inability to speak above a whisper. She was a clinic patient and was emaciated and showed the terrific strain of life. On account of her ignorance it was impossible to analyze her by the usual methods and no cause for the loss of voice could be uncovered. Various methods of treatment then in vogue were tried but without success. It was finally determined to try the effect of light etherization. It was argued that possibly during the excited stage of anesthesia the patient would cry out and if the crying could be continued until consciousness returned the speech mechanism might be restored to normal. The patient was willing to cooperate and light anesthesia was induced. As predicted the patient began to mumble during the excitement stage and finally cried out rather suddenly in an extremely loud tone, "God damn you, John, I won't call you." The anesthesia was immediately stopped. The patient was crying and talking at the time that she regained consciousness and her speech was restored to normal.

With the patient's statement as a clue and with the patient's cooperation, it was rather easy to reconstruct her story. Her husband was a drunkard and many times came home late

and intoxicated. In the morning it was necessary to call him many times before he was able to arouse himself sufficiently to go to his work. It was her practice to have the entire breakfast prepared prior to calling him. It was not unusual for the husband to quarrel with his wife and occasionally strike her for no apparent reason. She suffered many body and facial bruises as the result of his temper in the morning. She told us that on one occasion her nose was broken. She eventually became extremely fearful about awakening him because it would mean verbal abuse at least and sometimes physical violence. In view of the fact that her children came down to breakfast at the same time it was impossible for her to run to the second floor to call him but it was necessary to yell to him on several occasions before he would be awakened. With the onset of the aphonia, of course, she was unable to call her husband. She noted that since her loss of voice her husband had been more solicitous.

In an analysis of a case of this sort the underlying mechanism is very clearly brought out. The patient's hatred toward her husband as the result of his abuse can be very easily suspected from even a superficial study. Her desire not to awaken him in the morning was a very natural one. She, therefore, assumed the only defensive mechanism that she could to prevent arousing him in the morning. This served a double purpose. It incited a little sympathy in him and was a defense against calling him in the morning. It was, however, not a rational procedure because their livelihood was endangered.

A case of this sort is frequently easily cured of the presenting symptom of aphonia but the underlying family situation is not relieved thereby.

**Case II.**—A priest, aged fifty-five, was referred by Dr. Chevalier Jackson. His chief complaint was inability to speak above a whisper. He had been in charge of a large church in an adjacent city for many years. His work had been interesting and he had developed an implicit faith in his religion and his parish. He acted as counselor and as a friend to his people. He would help them with their business ventures and he had always found them honest. Just before the financial

depression he was asked to sign notes for two members of his congregation. He had done this on so many previous occasions that he did not hesitate. The depression came and both of the men for whom he had signed the notes lost heavily in their business ventures. Both disappeared from the city within a period of two weeks without leaving their forwarding addresses. It was, therefore, necessary for the priest to make good on both notes. When he came to see us he was paying small amounts to the bank every month for these notes. As the result of these dealings with people who had professed faith in religion, he had lost his belief in human beings and in religion in general. He, therefore, found his enthusiasm gradually waning and became more and more discouraged in his dealings with human beings. Suddenly an aphonia developed which was a means of escape from duties that were gradually becoming odious to him.

His aphonia was easily relieved by strong suggestion, re-enforced by faradic stimulation, but his faith in religion was still shattered. It has been several years since he has fully recovered his speech, but he tells me that he is unable to put into his work the enthusiasm that he did prior to the development of the aphonia.

**Case III.**—A school teacher of thirty was referred by Dr. Chevalier Jackson because of difficulty in speaking. In a detailed survey of her life these factors stood out. She lived in a small town; and her parents were at odds with each other. She did not live at home because of the family difficulties. Her family insisted on her telephoning them every day. She was ashamed of what was going on because of the scandal that was caused by her parents' marital difficulties. She also felt that it was spoiling her matrimonial chances. She was also a Sunday school teacher and she felt somewhat abashed to talk on religion and conduct to her Sunday school class in view of everyone's knowledge of her own family difficulties. She was ashamed to go out into public places. The conditions preyed on her mind to such an extent that she became seclusive. With the onset of the aphonia, however, her one problem was solved, although her other problem of earning a livelihood was jeopardized.

Assured by Dr. Jackson and his staff that there was no organic difficulty associated with her loss of voice, it was very easy to effect an almost immediate relief of the aphonia by strong suggestion. Frank discussion of her problem had the effect of giving her a different outlook on the entire situation. She left Philadelphia completely relieved of the hysterical symptom and with an indifference to her family problems because of her realization that she herself was not to blame for the dissensions between her parents.

**Case IV.**—Mr. W. was referred by Dr. Chevalier Jackson because of aphonia. The patient was a minister. He also did a great deal of singing and talking. He had been engaged in this type of work for about twenty-three years and had had no difficulty until approximately two years before we saw him. He noted gradually that it required more and more effort for him to speak. He was compelled to give up his work in February of 1935 because he found that he was unable to speak above a whisper. He consulted many throat specialists and was told by some that he had laryngitis. No improvement resulted from a great deal of treatment, including local applications, and osteopathic and chiropractic adjustments. He found that when he was singing as a guest in another city his speech was improved but in his own church his difficulties became markedly intensified. With this clue the family situation was gone into very carefully. He confessed that there was considerable difficulty with his wife. She was sexually frigid. About ten years before the onset of his difficulty, his wife engaged a boy of sixteen to help with the housework. He was not suspicious of the boy until a few years later when he came upon him and his wife suddenly and found them embracing and kissing. His wife's excuse was that her feeling for the boy was that of a mother. It was only after considerable wrangling that his wife permitted the boy to be discharged. She kept in communication with him for a period of about three years. The patient's mother-in-law, who was living with them, had frequently warned him about her daughter's infidelity. After the boy left the house he proceeded to discard the entire matter from his mind, but later his suspicions became directed against a man who was having dif-

difficulties with his own wife. On several occasions the patient found his wife in rather compromising situations with this man, for whom she admitted a great deal of sympathy in view of his marital difficulties. She planned and made trips to New York with him and many gifts came to the house from this man. There was no doubt in his mind that his wife was maintaining a clandestine affair.

During the time while he was away from his home his mother-in-law would occasionally write him letters airing her suspicions to him about her daughter. This would have the effect of disturbing him to such a point that it interfered with his work. Gradually his speech difficulty became so great that he was unable to carry on his work and remained at home doing odd jobs not connected with church affairs.

It was not difficult to relieve this patient of the presenting symptom of aphonia, but it was extremely difficult to acclimate him to what was going on at home. There was financial difficulty because of his inability to work and, in addition, his children were suffering because of the tense family situation. The patient has since left Philadelphia and has gone to a distant city to do another type of work not associated with the church, which does not demand vocal exertion. His wife is not with him.

A differentiation from malingering or feigning is necessary in every case of hysterical aphonia. To state glibly that hysterical aphonia is the result of an unconscious repression and malingering a conscious one does not help in their clinical differentiation. It is true that most persons tend to exaggerate their complaints and particularly so when the question of compensation comes into play. This, however, is not malingering in the psychiatric sense. The true malingerer consciously tries to simulate signs and symptoms for the purpose of monetary gain or to evade responsibility. The fundamental psychologic distinction is that the malingerer consciously attempts to deceive while in the hysteric the manifestations are unconsciously determined and beyond his control. Mutism is a much more common form of malingering than is aphonia. A careful survey of the entire clinical picture will usually suffice to make a distinction, although at times even the most expert may be baffled.



As a general rule the malingerer is not anxious for medical examination because he fears detection. The hysteric, on the contrary, usually welcomes medical study. Frequently the malingerer can be caught off guard when he believes he is not being watched. It is not infrequent for the person to talk when he is not aware that he is being observed medically. A hysteric cannot be caught "off guard" in this way.

A great many psychologic "tricks" have been devised to "catch" the malingerer. During the World War it was not uncommon to find malingering in the drafted men. Psychologic tricks were devised to confuse the person during the test such as dropping a coin in back of the person who claimed deafness; two-colored glasses when blindness in one eye was claimed, and so on.

A thorough knowledge of the neurologic and psychiatric manifestations and thorough study of the patient will serve as the best differentiating medium between hysteria and malingering.

In the treatment of hysterical aphonia a sharp distinction must be made between the treatment of the presenting symptom, the aphonia, and the treatment of the underlying condition, the hysterical personality.

In the treatment of the aphonia the therapist must have a combination of tact, art, self-assurance and, last and not least, knowledge. Yet with all of this the inaccessibility of the patient himself may prevent a good result. There is no doubt that the personality of the therapist plays a tremendous rôle in the treatment. That actual knowledge is not a requisite can be judged from the excellent results obtained by quacks in the treatment of conditions of this type.

The tact of the therapist is shown by his handling of the patient. The patient will resent any suggestion by doctor or relative that his condition is "imaginary." It often provokes greater resentment and renders the problem much more difficult, if not impossible. A complete study of the patient must be made in order to convince him that his problem has been taken seriously. This will include a detailed history, consisting of a social and psychiatric study and a very careful physical examination. It must be explained to the patient that the fact that nothing of an organic nature is found to account for the

symptoms does not mean that he is not ill. It must also be carefully explained to the patient that a nervous disease is like any other illness and it requires treatment for its relief. It is wise, at times, when the patient is intelligent, to give him an insight into the mechanism of hysteria and explain the rôle played by the various emotional factors. This will dispel for the patient the fear that his condition is entirely the result of his imagination. An error is often made to concentrate the patient's attention on somatic conditions. To claim that an aphonia is the result of "laryngitis" is to give the patient a self-satisfying explanation for his complaints. No local instrumentation or operation should be suggested because they only tend to perpetuate symptoms which should be easily removed by psychotherapeutic measures.

The method and means of therapy will vary with the individual therapist. Any therapeutic measure which promises relief is indicated and justified. There is no objection to the use of medicaments, electricity or hypodermic injections, provided the physician realizes that he is using these as suggestive measures to influence the patient psychically. No two patients can be treated alike. The therapist must realize, however, that he cannot expect the medication or other suggestive measure to clear up a severe mental conflict or to adjust some family situation.

Suggestion plays the major rôle in the treatment, but the susceptibility of these patients to suggestion has been over-emphasized. It is true that a symptomatic cure of hysterical aphonia can easily be accomplished with suggestion alone, but we should go beyond this. For immediate relief of the presenting symptom, strong suggestion or even hypnosis may be employed, but the goal is to find the forces which have caused the repression. One should not be satisfied with the clearing up of the hysterical manifestation but should probe into the mechanism of the condition, without subjecting the patient to a prolonged psychoanalytic procedure. It is necessary in most cases to complete the study and give the patient an insight into the mechanism of the problem as quickly as possible. The personality defect must also be subjected to minute investigation and must be corrected if at all possible. It is to be stressed that most of the patients can be treated in one's

office without interruption of their routine of work. This is also a very important point because not only must the patients' time be occupied, but also they are earning enough to take care of their obligations. They also have impressed on them the fact that they are not sick enough to stop their work.

It must be recognized that the patient had made a "flight into disease" as a means of solving what to him had become an intolerable situation. All the facts of his difficulties must be obtained so that the therapist will know the conditions from which the patient is making an escape. A frank discussion of his problem is essential. It must be realized that the therapist is unable to adjust family difficulties or financial reverses, but he can reeducate the patient to reconsider his problems and to readjust himself to conditions. It is manifestly impossible for the therapist to correct an erring wife, as in Case IV, or to cure the alcoholic cravings of the husband of our first patient. Sufficient time should be taken with the patient to go over the entire situation, to make the patient more satisfied with his lot, to try to get him to seek other outlets for his energies, and to take an interest in outside affairs. A good many of our patients have been school teachers who have reached the age where marriage is a forlorn hope. To hold out hope to patients of this sort for matrimony is wrong, but to educate them to be satisfied with their lots is essential.

As a rule a prolonged psychoanalysis is not indicated in these cases. While intensive analysis revealing the basic psychogenic factors may be desirable in certain cases of hysteria, it is unnecessary and frequently undesirable in the great majority of these hysterical individuals who show but one symptom of that disease. At no time should the patient be accused of not desiring to get well because it indicates a poor understanding on the part of the doctor. Even when this is suspected it should be made part of the psychotherapeutic procedure and not the topic for argument or accusation.

As the patient's entire life is reviewed before us, we can frequently give the patient a little insight into his own problem by appropriate hints during the recital. This is frequently part of the therapeutic procedure and is of value in helping the patient to solve his problem.

My own procedure in a case of hysterical aphonia is to obtain a detailed history from the patient at the first consultation. A great many significant facts can be uncovered in the first interview, but at times repeated interviews are necessary before the complete story can be obtained. The entire sequence of events leading to the loss of voice can frequently be disclosed in the course of five or six interviews. During this time treatment for the somatic symptom is undertaken after a thorough physical study. As a rule these cases have been referred by laryngologists who have completely ruled out any organic involvement. Strong suggestion is given and augmented when necessary by faradic stimulation of the muscles of the throat. As a rule complete relief of the aphonia has been obtained in the course of two or three treatments. Our most difficult cases have been those who have had a peculiar grunting type of speech rather than a true aphonia. This condition might more appropriately be called "hysterical dysphonia." This has usually become so deeply ingrained that an actual habit has been established of talking in this peculiar way.

In the meantime, the rest of the interview is taken up with delving into the history to determine the psychogenic factors responsible for the condition. In our experience sex has not played the dominant rôle. A very frank discussion with the patient is often conducive to a marked change in the patient's attitude toward his own problems. I try to get the patient to view his own condition from an impartial angle and will frequently ask him to give advice to someone else under the same conditions. It has usually not been necessary to resort to intensive psychoanalytic measures because the aphonia has most often followed close upon the precipitating situations.

As a rule our results in the treatment of hysterical aphonia have been excellent. In 1 or 2 cases seen within the last two or three years where relief of the symptoms has not occurred promptly, prolonged psychoanalytic treatment in other hands has also been unsuccessful. Best results are obtained in cases where the aphonia has been present but a short time. As already stated, those cases with the grunting or "bearing-down" type of speech are the most resistant, and particularly so if the condition has been present for months or years prior to therapy.

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### GONORRHEA IN WOMEN

I SHALL outline in this discussion some important points in the diagnosis and treatment of gonorrhea in women. Theoretic consideration will be avoided as much as possible so that this outline may serve as a safe and practical guide which can be followed by every physician who would undertake treatment of this important and serious condition. Gonorrhea of the internal genitalia will not be considered except in a prophylactic way and no thought will be given to gonorrhea in the preadolescent female.

#### ACUTE GONORRHEA

Gonorrhea may be an acute diffuse infection of the external genitalia when observed early in its course, or it may be a latent or chronic infection when observed late in its course. The acute stage of gonorrhea is usually easy to diagnose by a complete history taken from the patient or her consort, and an examination of the parts affected. Very often the patient suspects the condition and will tell you the source of her infection. The usual history is that exposure occurred from one to seven days before the symptoms were observed.

The symptoms of acute gonorrheal infection are often mild and not characteristic. There is some irritation about the external genitalia with burning and itching; if the urethra is infected there will be some dysuria; if the Bartholin's gland is infected there may be pain. A vaginal discharge may be present, but it has very little significance so far as a specific symptom is concerned. The symptoms may be so transitory that they have escaped the notice of the patient unless something occurs which calls her attention to her slightly unusual condition.

The examination of the patient is the most important part of the consultation. Before the description of the examination is given, I shall discuss briefly some of the habits of the gonococcus and the reaction which it produces in its host.

The gonococcus is a gram-negative diplococcus first described by A. Neisser in 1879. It is recognized in smears taken from the infected areas when stained by the Gram technic or some modification of it. The smears contain pus cells and the gonococci appear as two bodies like coffee beans with opposing flat surfaces with some organisms grouped inside of the pus cells and others free in the smear. The intracellular organisms are most significant.

The habit of the gonococci is to thrive on moist epithelial surfaces of the columnar type. For this reason the generalized infection about the genitalia persists for only a short while and usually complete subsidence of it has occurred within two or three weeks. The infection finally localizes in the urethral glands, Bartholin's gland, and the endocervix. Because these glands and the endocervix are lined by columnar epithelium, and because the areas drain badly, the infection persists indefinitely in them.

**Examination of the Patient.**—The patient is arranged for gynecologic examination on a suitable table. The bladder should have been emptied before the examination is undertaken. By this means the urethra will have been cleared of epithelial cells and degenerated pus cells. With good light the vestibule of the vagina is examined for any evidence of infection. Skene's tubules, the urethra, and Bartholin's ducts are minutely inspected, and after a thorough investigation of the parts, the secretion is removed from the vestibule of the vagina and from the urethral glands, and transferred to a clean glass slide by means of a wooden or metal applicator. The applicator should not be wrapped with cotton because of the confusion which the cotton fibers may cause in the study of the smear. These stained smears are studied at the time of the examination by the physician himself, or under his personal supervision. The presence of pus cells in smears taken from these areas is very significant of a gonorrheal infection either acute or latent, and if the examination is done carefully, the gonococci will almost surely be found. Many organisms

will be seen if the infection is recent, and only a few if the infection has been of long enough standing to have limited itself. If the gonococci are found in smears from the vestibule of the vagina and urethra, no further examination is necessary to make the diagnosis, and a more complete examination may spread the infection from the external genitalia to the endocervix which may be free of the infection.

**Treatment of Acute Gonorrhea.**—The treatment of acute gonorrhea is based on two premises, the first to manage the patient so that her infection will localize in the urethral glands, the endocervix, and Bartholin's gland; the second, to prevent so far as possible the extension of the infection to the fallopian tubes and the pelvic peritoneum. These aims may be accomplished usually by the following plan: a simple sedative should be given the patient, such as phenobarbital,  $\frac{1}{4}$  grain, and sodium citrate, 30 grains, every four hours; this mixture will alkalinize the urine and prevent some of the discomfort of which she may complain. Local treatment should consist of keeping the parts clean with some mild antiseptic soap and a vaginal douche of bicarbonate of soda (tablespoonful to 1 quart of warm water) once or twice daily. The douche should be given with the patient in the supine position with her hips slightly elevated and the water container placed 24 inches above her body. High-pressure douches are absolutely to be avoided. Specific directions should be given the patient to avoid all types of physical exertion or activity which would increase intravaginal pressure, such as coitus, dancing, swimming, diving, heavy lifting, and sexual stimulation. Topical applications of antiseptics to the infected areas should be avoided because of the danger of causing an extension of the infection to the internal genitalia, and because the antiseptics may inhibit the natural reaction of the tissue to the infection. Our aim in the management of these patients is to aid them and their own forces to overcome the acute infection. Good food, plenty of rest, and thorough elimination from the bowel are a necessary adjunct to this routine.

After a few weeks or longer of this routine, the acute infection will have become latent, the symptoms will have subsided, and the patient will not be conscious of her trouble.

In treating acute gonorrhea in women as outlined, we have recognized that it is essentially a self-limited infection and that our whole problem in the acute stage is to make the diagnosis, and to prevent as far as possible the extension of the infection to the internal genitalia.

### LATENT OR CHRONIC GONORRHEA

Latent or chronic gonorrhea is the type of infection which is most often seen. It is the term used to describe the infection after it has localized in Skene's tubules, urethral glands, Bartholin's gland, and the endocervix. The infection in these focal areas may persist indefinitely unless very active means are used to destroy it and, as long the infection persists, the patient is infectious to herself and to her consort.

**Diagnosis.**—The diagnosis of latent gonorrhea is quite difficult at times, especially when there is no known background of an acute infection. Smears should be made of the secretions taken from the urethra and from the cervix after the bladder has been emptied. To obtain smears from the urethra, it is massaged vigorously against the under surface of the symphysis and the expressed secretion transferred to a glass slide. If no organisms or pus cells are observed in the smears taken at the first examination, it should be repeated in twenty-four hours. Very often the trauma produced by the first examination will cause enough tissue reaction so that twenty-four hours later organisms or pus cells can easily be discovered. The presence of pus cells in the smears taken from the urethra is very significant of a latent gonorrheal infection and if one is persistent enough and thorough in examining the smears, gonococci are almost sure to be seen. Smears of the secretion from Bartholin's gland should also be secured and studied in the same manner.

The smears from the cervix should be taken with the utmost care. The cervix is exposed and all of the vaginal secretion gently cleaned from the portio, and the secretion from the cervical canal transferred to a glass slide by means of an unwrapped wooden applicator. The presence of pus cells in the smears indicates an endocervicitis which may be gonorrheal in origin. The gonococci are sometimes quite difficult



to find in the latent cases, but usually with care an occasional organism can be discovered. A good working premise is that a latent endocervicitis which accompanies a latent infection of the urethral glands is gonorrheal and the infection must be treated accordingly.

**Treatment.**—The Skene's tubules and the urethral glands are isolated with small probes and located very carefully before anesthetizing the urethra. A cotton-wrapped applicator saturated with a 10 per cent solution of cocaine hydrochloride is then applied to the urethral canal for five minutes. After the urethra has been properly anesthetized either a small tip cautery, or the electrode of a diathermy generator, is inserted into the isolated tubules, and each tubule is then coagulated. Complete healing of the coagulated area occurs in about twenty-one days after which a careful search for other foci about the urethra should be made and, if any are found, destroyed in the same manner.

At the time of the treatment of the urethra, the cervix is exposed and the infected endocervical tissue is destroyed. This may be accomplished by simple cauterization, coagulation, or endocervical resection. No anesthetic is required for cauterization or tissue coagulation of the cervix; however, an anesthetic is necessary for endocervical resection. Cauterization of the endocervix is by far the most easily accessible means of treatment but does not always seem to be so adequate as the other procedures. The reason, perhaps, is that not enough of the endocervical tissue can be destroyed without the occurrence of stenosis. Tissue coagulation seems to be a very satisfactory method. The electrode should be about 2 mm. in diameter; the current used should be adjusted so that carbonization and too deep destruction of tissue do not occur and the whole circumference of the cervical canal coagulated for about three quarters of its length. Endocervical resection may be undertaken and accomplished by the method described and popularized by Hyams, or it may be done by the operation described by Sturmdorf. Both of these methods are effectual if properly executed. They require, however, the facilities of an operating room and a general anesthetic, and certainly in most instances the other procedures will be quite as satisfactory.

The treatment of Bartholin's gland when it becomes necessary is sometimes a difficult problem. As a rule an abscess develops which must be incised and drained. If the whole of the gland has been destroyed by the infection, the area closes by granulation and no residual infection remains. If part of the gland remains, however, after the infection and the duct is closed, another abscess may form or a Bartholin's cyst may develop.

After destruction of the focal areas of infection, the patient should be instructed to carry out the same routine as prescribed for acute gonorrhea. The treated areas should be examined once or twice weekly, and if the slough seems to be preventing drainage of the parts, it should be separated very carefully.

A profuse offensive discharge follows these treatments in about four days, and some bleeding may occur when the slough separates. These symptoms may persist for ten days, and may cause the patient considerable anxiety. They are, however, the natural sequence of the treatments and can be managed usually without difficulty by warning her to anticipate them.

Complete evolution of the treated areas occurs in about four weeks. The treated Skene's tubules and urethral glands are replaced with fibrous tissue and their location is covered with squamous epithelium. The destroyed endocervix is replaced largely with squamous epithelium of the vaginal type. During evolution of the treated area of the cervix, there is a potential danger of stenosis occurring. This, however, does not occur frequently unless the treatment has been too vigorous or of a fractional type. If it should occur, its management becomes a problem which cannot be considered here.

**Diathermy Treatment.**—Diathermy treatment to increase intravaginal temperature must be mentioned as a means of treating endocervical infections. The methods are varied and some have considerable merit. The so-called "Elliott douche" and the short-wave diathermy machine with a special vaginal electrode are among the procedures used for this purpose. These are special appliances, however, and their use in the treatment of latent gonorrhea is not sufficiently standardized to be outlined for general use.

## PROOF OF CURE

To know when patients are cured and when it is safe for them to resume sexual relationship is the most important obligation one assumes in the management of gonorrhea in women. The disease can be cured and we must have some standard for proof of cure. The conventional standard for proof of cure based on the absence of the gonococci in three sets of smears taken at different intervals is very unreliable because occasional organisms, which could easily be missed in a very careful examination of smears, might well be responsible for a new infection in the individual or her consort. Cultures for the gonococci are not practical because of the contaminating organisms in the material secured for culture. The complement-fixation test is not sensitive enough to determine lower genital infection.

The method to determine cure, which is applicable in most cases, is one which I have used for a long period of time in my own work. I have been able to check on it a number of times and have come to regard it with considerable confidence. The method is based on the premise that the secretion from a noninfected urethra, Bartholin's gland, or cervix contains no pus cells. The reaction of these areas to the gonococci is an inflammatory one, and the secretions will therefore contain pus when infection is present. Smears are made at intervals of the secretions taken from these focal areas with considerable care, and each smear is examined for pus cells. If the smear contains pus cells, I presume that the patient is not cured, and further treatment and observation are necessary. Conversely, I presume that if pus cells are absent in the smears taken from these areas, no inflammation is present and the patient is no longer infectious. This whole course of treatment and observation will require considerable time, very often six months or more.

## CONCLUSIONS

I have outlined methods of treatment of gonorrhea in women. They are based on the following conceptions:

1. That the acute diffuse infection is self-limited.
2. That infection of the fallopian tubes and pelvic peritoneum can be prevented in most instances if no active treat-

ment is undertaken in the acute attack and if the patient is directed to avoid physical activities which increase intravaginal pressure.

3. That the focal areas of infection can be destroyed in latent gonorrhea.

4. That the absence of pus cells in the secretion from the lower genital tract is the best proof that these patients are no longer infectious and therefore are cured.

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### PRACTICAL ASPECTS OF VITAMIN B DEFICIENCY

RECENT investigation of vitamin B deficiency carried out in this clinic has yielded information of importance to the practicing physician. From experience obtained in such study it is believed that a moderate deficiency of vitamin B is by no means rare; that clinical evidence of such deficiency can be recognized as a characteristic syndrome, and that the factors which predispose to the development of such deficiency are many and more varied than previously realized. Most of the information concerning the properties and functions of vitamin B has been obtained in the chemical and biologic laboratories and it is from these sources that the ultimate understanding of its physiologic rôle will come. It will be a long time, however, before this type of information is available in such form as to be of practical importance in clinical medicine and, in the meantime, it has seemed desirable to study the clinical aspects of vitamin B deficiency under as carefully controlled conditions as possible.

It is now known from biologic experiments that vitamin B is not a simple substance but is composed of several different fractions. The best-defined fractions are as follows:

Vitamin B<sub>1</sub>—concerned chiefly with the integrity of nervous tissue and probably acting as a catalyst in cellular oxidation processes.

Vitamin B<sub>2</sub> (G)—which is now subdivided into the following: (a) lactoflavine—necessary for normal growth, (b) vitamin B<sub>2</sub>—which prevents dermatitis in animals, and (c) pellagra-preventive factor—important in human pellagra.

Vitamin B<sub>4</sub>—concerned with the integrity of nervous tissue and probably important for normal bone-marrow function.

Knowledge obtained by a study of these separate fractions, made chiefly with animals, does not account for all of the functions of the vitamin B complex as observed in human beings and it is, therefore, with the rôle of the complete vitamin B\* complex that the clinician is now concerned. Much information has been circulated, chiefly by commercial houses, concerning the functions of vitamin B in humans. Many of these claims are extravagant and result in misapplied therapy. They arise from two general sources of error. First, results obtained from animal experiments, designed to test the effect of one of the separate fractions of vitamin B in a specific animal, have been applied uncritically to human beings; secondly, erroneous impressions are often gained from inadequately controlled observations on patients. It is only through very careful control of the environment of the patient and through prolonged observation that any adequate new information can be obtained on nutritional subjects of this type. It is the aim of this communication to give briefly proved facts concerning vitamin B deficiency in humans and to show by the presentation of certain representative cases how this information has been of assistance in treatment of patients. These observations have been confined to adults.

#### CLINICAL MANIFESTATIONS OF VITAMIN B DEFICIENCY

Symptoms and physical signs of mild vitamin B deficiency have been ascertained<sup>1, 2</sup> through prolonged study of patients subsisting on a diet of known composition. The changes encountered were referable chiefly: (1) to the gastro-intestinal tract; (2) to the nervous system; (3) to the blood and, in certain instances, (4) to the cardiovascular system.

1. **Gastro-intestinal Phenomena.**—The tongue is usually involved first, becoming sore sometimes without alteration in appearance, or there may be redness or loss of papillae unaccompanied by unusual sensation. Changes in the tongue have been noted as early as twenty-one days after beginning a diet deficient in vitamin B and have always preceded the

\* The term "vitamin B" is used in this communication to denote the entire B complex; individual fractions are referred to separately

development of other gastro-intestinal symptoms which are, characteristically, heart burn, a sense of fulness in the abdomen, loss of appetite and either constipation or diarrhea. These symptoms are accompanied by roentgen evidence of altered tone in the gastro-intestinal tract, the stomach becoming atonic and the small intestine displaying irregular areas of increased and of decreased tone. No characteristic alteration in the gastric acidity has been demonstrated. The absorption of protein from the intestinal tract has been studied in one patient and evidence of impairment obtained. Other investigators<sup>3</sup> have associated ulceration of the gastro-intestinal tract with deficiency of vitamin B. There is convincing evidence<sup>4</sup> that ulceration of the intestinal tract takes place in animals subsisting on a diet deficient in vitamin B, but, although manifestations of deficiency certainly are frequent in patients suffering from such conditions as colitis, it is difficult to be certain whether destruction of the intestinal mucosa is the result or the cause of the deficiency.

**2. Neurologic Phenomena.**—Paresthesias, particularly in the lower extremities, are an early complaint. Unless the deficiency is corrected these are followed by objective neurologic signs, the earliest of which is impairment of vibratory sense in the toes. The duration of the perception of vibration is at first decreased and later the sensation is lost.

Susceptibility to fatigue is an early symptom which appears at approximately the same time that paresthesias are first felt and changes noted in the tongue.

**3. Hematologic Changes.**—It has been possible to demonstrate alterations in the peripheral blood indicative of impaired bone marrow function in pregnant women<sup>2</sup> whose consumption of vitamin B was inadequate to meet the requirements of late pregnancy. The anemia resembled in every important respect the macrocytic anemia of pernicious anemia, sprue<sup>6</sup> and tropical macrocytic anemia.<sup>7</sup>

Ecchymoses without a history of trauma are frequently seen especially in the lower extremities.

**4. Edema and Cardiovascular Phenomena.**—Edema has been a prominent finding in the patients studied. It is not accompanied by cardiovascular or renal changes sufficient to explain it, and although, in certain instances, associated

with decreased serum protein, it is not strictly dependent on the serum protein level.

Cardiovascular changes are variable and never striking. The majority of patients complain of dyspnea on exertion and a certain number of them have shown a persistent tachycardia which has been associated with roentgen evidence of prominence of the pulmonary artery. There are no characteristic electrocardiographic changes. The marked cardiovascular signs in severe deficiency, *i. e.*, loss of peripheral vascular tone, hypotension and right-sided heart failure,<sup>8, 9</sup> are well known but should not be expected in cases of mild deficiency.

There are at present no satisfactory clinical tests<sup>10, 11</sup> which indicate the presence of early vitamin B deficiency, and the physician must, therefore, make the diagnosis from the manifestations listed above. It is apparent that no one of these indicates specifically the presence of deficiency, but it is, rather, the occurrence of the syndrome as a whole which suggests the condition. The clinician should be cautioned against attributing isolated phenomena to deficiency of this nature since it has been our experience that, although the severity of the different manifestations varies among individuals, no manifestation, later satisfactorily proved to be due to vitamin B deficiency, has occurred entirely independently of the others.

#### REQUIREMENTS FOR VITAMIN B

The vitamin B requirement of man varies according to certain known factors and also to some as yet unidentified ones. Thus a diet which may be adequate for one man will be quite inadequate for his neighbor, depending upon individual requirements. For this reason, in order to determine the likelihood of a person developing vitamin B deficiency, although it is necessary to know the approximate vitamin content of the diet, such knowledge alone will not suffice.

The minimum vitamin B requirement of a normal individual theoretically varies directly according to his weight and to his total metabolism.\* Thus if a man's weight and his basal metabolic rate remain constant, his vitamin B require-

\* The Cowgill formula<sup>12</sup> by which the theoretical vitamin B requirement may be calculated in terms of milligram equivalents of vitamin B (see below) is: vitamin B calories = 0.0000284 Gm.



ment will vary directly according to the number of calories he eats every day. These theoretical requirements have been corroborated by a study of the diet of alcoholics showing signs of deficiency<sup>13</sup> and by observation of a group of pregnant women whose dietary content of vitamin B was known.<sup>2</sup> In these women signs of deficiency developed when increase in weight resulted in theoretical requirements for vitamin B which exceeded the dietary intake. It has been found, also, that pregnant women who display a predilection for high caloric foods which are low in vitamin B, and so increase their caloric intake excessively, are predisposed toward the development of vitamin B deficiency (Case I). There is some evidence,<sup>1</sup> also, that if the chief source of calories is in carbohydrate the patient is more likely to develop deficiency than if the fat content of the diet is high. For some as yet unexplained reason fat spares the vitamin B,<sup>14</sup> permitting the more effective use of a small quantity of the vitamin.

The normal individual's minimum vitamin B requirement can be determined with fair accuracy; the optimum is less well defined. From animal experiments<sup>15</sup> it may be inferred that this is somewhere about five times the minimum and it has been our experience that the average person who has shown signs of vitamin B deficiency, but who is otherwise normal, can be relieved of deficiency and maintained in excellent health by this dosage.

There are many factors which increase the individual's vitamin B requirement above the normal and predispose him to the development of deficiency. Thus anything which increases the basal metabolic rate: hyperthyroidism (Case II) or fever will increase the need for vitamin B. Excessive muscular work, by increasing the total metabolism, increases the vitamin B requirement. Excessive caloric intake or excessive carbohydrate intake, as noted above, will increase the demand for vitamin B. Unusual gain in weight will result in evidences of deficiency if the vitamin content of the diet is not increased proportionately. This is probably the chief factor in the increased demand for vitamin B during pregnancy although altered endocrine function may play a rôle in some as yet unexplained way. The fact that evidence of vitamin B deficiency does not occur more frequently among the mal-

nourished is probably due to a combination of low total caloric intake and reduced body weight. It has been our experience that age plays some rôle in altering the vitamin B requirements. Elderly people, especially women, frequently show evidence of deficiency when the diet is apparently adequate (Case III). Whether this is a failure of absorption from the intestinal tract or is associated with some altered endocrine function is as yet undetermined. The effects of surgical procedures upon the development of signs of deficiency have been of particular interest to us. We have noted frequently that certain patients, who preoperatively show few or no signs of vitamin deficiency, following operation develop frank deficiency. There are several possible explanations for this fact. Fever increases the vitamin B requirement and in an individual whose vitamin intake has for any reason been impaired prior to operation, fever occurring postoperatively may result in very rapid development of deficiency, particularly if the intake of food is inadequate during this time. Thus, surgery of the gastro-intestinal tract is most often followed by evidences of vitamin B deficiency, the subjects of such surgery frequently having had a minimal vitamin intake prior to operation, *viz.*, pyloric stenosis patients, or having suffered failure of absorption of the vitamin through prolonged diarrhea: cases of colitis (Case IV), terminal ileitis, tuberculosis, etc., and such surgery often being followed by prolonged periods of inadequate food intake.

Decreased absorption from the intestinal tract will result in deficiency even in the face of adequate vitamin intake. Any prolonged diarrhea, regardless of the cause, is likely ultimately to result in deficiency. Any decrease in the available absorbing surface of the intestine will produce the same result. Alteration of gastro-intestinal secretions may influence the efficiency of absorption of vitamin B. We have noted that patients with achlorhydria frequently show evidence of deficiency even when the dietary intake is adequate (Case III).

#### SOURCES OF VITAMIN B

1. **Dietary.**—It is important that the clinician know the chief dietary sources of vitamin B. As has been pointed out, however, the vitamin content of the diet does not alone deter-

mine whether a given patient will develop vitamin B deficiency. A casual analysis of the diet may, therefore, lead to an erroneous impression unless the other factors which may influence the development of deficiency are kept in mind. It should be emphasized also that the concentration of the vitamin in a given food is important and simple qualitative analyses are often misleading. For example, while dried milk is an excellent source of vitamin B<sub>1</sub>, in whole milk the concentration of the vitamin is reduced to one seventh of that in the dry state and milk as ordinarily consumed, therefore, becomes a relatively poor source of the vitamin. It is important also to realize that the vitamin content of foods varies, in the case of animal foods, according to the diet of the animal and, in the instance of vegetables, according to the soil and atmospheric conditions. The vitamin B content of yeast, for example, varies enormously depending upon the type of yeast and the conditions under which it is grown. For these reasons it is desirable, when vitamin B deficiency is suspected from clinical evidence, to administer the vitamin in the form of preparations of tested potency.

The chief dietary sources of vitamin B may be found listed in detail in various texts,<sup>12, 16</sup> but if the following foods are kept in mind as the major sources of vitamin B in the average diet, they will serve as a fair working basis: liver, pork, kidney, beef, salmon, eggs, nuts, oatmeal, tomatoes, asparagus, artichokes, lima beans. Yeast and wheat germ are, of course, the richest sources of vitamin B, but since they are rarely included in the average diet they can hardly be considered dietary sources. In general, the various fractions of the vitamin are found in the same foods with the following exceptions: liver is an excellent source of vitamins B<sub>2</sub> and B<sub>4</sub> but contains negligible quantities of vitamin B<sub>1</sub>; egg white is also rich in B<sub>2</sub> without demonstrable amounts of B<sub>1</sub>.

The ideal diet, then, from the standpoint of vitamin B requirement is one which contains the calculated normal total number of calories (approximately 20 calories per pound for a person engaging in moderate activity), an average normal intake of carbohydrate (60 per cent of total caloric consumption to be derived from this source) and sufficient vitamin B to supply five times the minimum requirement. This latter

figure can be calculated from the Cowgill formula but in general will be covered if the individual consumes liberal quantities daily of at least three of the rich sources of vitamin B listed above.

**2. Special Sources.**—As has been stated, if vitamin B deficiency has developed as indicated from the clinical signs, it is wise to employ immediately one of the special sources, the potency of which has been ascertained.

Much use is made of the term "units of vitamin B" in advertising commercial sources of the vitamin. In determining the dose of these substances it is important to know the value of the units in which the potency of a given preparation is reported. The "Sherman unit"\* is the one most frequently employed and refers to the amount of special vitamin B<sub>1</sub> or B<sub>2</sub> preparations necessary to maintain normal growth in rats.<sup>17, 18</sup> Although, as has been seen from the foregoing discussion, it is impossible to make any accurate generalization concerning the amount of vitamin B required by patients, it can be said that probably a safe minimum amount to include in the diet of the average adult is not less than 1000 Sherman units† and the optimum will be approximately five times that amount. The special sources are as follows:

(a) *Yeast*.—This is the most adequate source of the B complex. There are many commercial preparations of yeast on the market. In selecting one of these the clinician should remember that brewer's yeast is a very much more potent source of the vitamin than baker's yeast and thus a smaller

\* Other units sometimes employed in listing the potency of vitamin B preparations are:<sup>12</sup>

1. "Pigeon unit"—the amount of B<sub>1</sub> necessary to cure pigeons of polyneuritis. This unit contains ten times the amount of B<sub>1</sub> in the Sherman unit

2. "International unit"—the amount of vitamin B<sub>1</sub> contained in 10 mg of standard substance kept at the National Institute for Medical Research, London. This unit contains four times the amount of B<sub>1</sub> in the Sherman unit

3. Cowgill milligram equivalent—the amount of B<sub>1</sub> contained in 1 mg of a standard yeast powder. One milligram equivalent contains one fifth the amount of B<sub>1</sub> in a Sherman unit.

† Sherman units have been worked out only for vitamins B<sub>1</sub> and B<sub>2</sub>. The dose of a substance should be calculated so that a minimum of 1000 units of either fraction is given. In such a dose it can be assumed that other fractions are included in adequate minimum amounts unless the substance is known to be poor in some fraction.

quantity of material from this source will answer the patient's need.

The following brewer's yeast preparations have been used extensively in experimental work and their potency in all essential fractions of vitamin B assured:\*

1. Yeast-Vitamin Powder (Harris).—A minimum dose of this substance is 5 Gm. and the probable average optimum is 25 Gm. or approximately 3 level tablespoonfuls daily.†

2. Vegex (an autolyzed yeast preparation known also as Marmite).—A minimum dose of this substance is 40 Gm., or 5 teaspoonfuls daily.

(b) *Wheat Germ*.—This substance is, next to yeast, the most complete source of the B complex. It is, however, richer in vitamins B<sub>1</sub> and B<sub>4</sub> than in vitamin B<sub>2</sub>. For this reason, when used in cases that show evidences of deficiency it is wise to employ a supplement which is rich in vitamin B<sub>2</sub>.

The wheat germ preparations which have received experimental investigation are:

1. Bemax—40 Gm. or 9 tablespoonfuls of this substance are required daily to supply the minimum of 1000 Sherman units of vitamin B<sub>1</sub>.

2. Vitavose—76 Gm. of this substance are required daily to supply the minimum of 1000 Sherman units of vitamin B<sub>1</sub>.

(c) *Liver and Liver Extract*.—Liver is an excellent source of vitamins B<sub>2</sub> and B<sub>4</sub>. All extracts prepared for use in pernicious anemia contain these vitamins. Liver extract is equally effective when administered parenterally or by mouth but since it contains comparatively little vitamin B<sub>1</sub> this should be given separately.

Liver extract No. 343 (Lilly) has been used experimentally as an effective source of vitamin B<sub>2</sub>. When given orally 20 Gm. constitute the minimum dose. Intramuscularly 2 cc. of the standard extract daily have been effective but some patients require as much as 10 cc. daily to relieve signs of deficiency.

(d) *Vitamin B<sub>1</sub>* is now available in the pure, crystalline form. It is prepared by the Merck Company under the trade

\* The preparations referred to are those with which the writer has had personal experience and do not comprise a complete list of available materials.

† The approximate dose of these preparations is calculated on the assumption that they constitute the sole source of the vitamin.

name "Betabion" and by the Winthrop Company as "Betaxin." It is equally effective when administered intravenously or when taken by mouth; 0.5 mg. constitutes the minimum dose of this substance and the probable optimum is 2.5 mg. Although there is some evidence that certain neurologic lesions are relieved by the administration of this substance alone, in the present state of our knowledge it is unwise for the clinician to depend entirely upon this substance for relief of the manifestations of vitamin B deficiency.

(e) *Lactoflavine*.—This substance has been prepared in pure, crystalline form. It apparently contains a growth-promoting factor which is a component of vitamin B<sub>2</sub>. Like all the special preparations of separate elements of the vitamin B complex this substance is at present of value chiefly for experimental purposes and should not be employed by the clinician as the sole agent in the treatment of clinical deficiency.

When special sources of vitamin B are employed it is necessary to consider whether oral administration will be effective. If there is reason to believe that absorption from the gastrointestinal tract is impaired, or if the patient's requirement is so increased that he is unable to take the vitamin in sufficient quantity by mouth to meet his needs, then parenteral administration is indicated. Liver extract and crystalline vitamin B<sub>1</sub> administered parenterally to the same individual in adequate dosage probably will supply all the necessary fractions.

### CASE REPORTS

**Case I.**—V. W., twenty-one years of age, a white female, was admitted to the maternity ward on December 2, 1936, nine months' pregnant, complaining of easy fatigue, sore tongue, heart burn, headaches, dyspnea on slight exertion, edema of the ankles, and a sense of numbness in the toes. Blood pressure 132/100, pulse 85, red blood cells 3,220,000, hemoglobin 61 per cent (Sahli), serum protein 5.3 Gm. per cent. Urine: specific gravity 1.020, albumin 0, casts 0. There was marked edema about the ankles, tongue was red with some loss of papillae at the edges, vibratory sense was impaired over the toes. It was found that while the patient's diet had been quantitatively adequate her appetite had been excessive

and she had taken a preponderance of carbohydrate foods. She weighed 165 pounds, this being 13 pounds in excess of her normal weight for that period in pregnancy. She was put on a weighed diet of 3000 calories containing 300 Gm. of carbohydrate and given 30 Gm. daily of Yeast-Vitamin Powder (Harris). She improved steadily and was discharged on December 17, symptom free, without abnormal physical signs, blood pressure 130/80, pulse 70, red blood cells 3,980,000, hemoglobin 70 per cent, serum protein 6.4 Gm. per cent. Urinalysis was negative.

This case is presented as characteristic of a number of pregnant patients recently encountered in whom excessive gain in weight, excessive total caloric intake, or a preponderance of carbohydrate foods in the diet have resulted in the appearance of clinical signs which respond to vitamin B therapy. Certain of these signs sometimes resemble those of the so-called "toxemia of pregnancy." Further study of these two conditions is necessary to determine in how far there is a common etiologic factor.

**Case II.**—F. C., fifty-four years of age, a white female, was admitted to the surgical service on January 5, 1934. Onset of typical symptoms of hyperthyroidism in August, 1933, viz., tremors, sweats, weakness, loss of weight. In November she suffered an attack of "grippe" and, following this, in addition to the continued symptoms of hyperthyroidism, she began to complain of the following which were prominent symptoms on admission: anorexia, epigastric discomfort, alternating constipation and diarrhea, sore tongue, dysphagia, shooting pains in the lower extremities, swelling of the ankles, and considerable mental confusion. On admission blood pressure 116/42, pulse 120, weight 100 pounds (normal, 144), basal metabolic rate + 63 per cent, red blood cells 3,500,000, hemoglobin 62 per cent, serum protein 6.5 Gm. per cent. She was obviously extremely ill, irritational, showed evidences of marked weight loss. The tongue was very red, smooth and was extended with a coarse tremor. The thyroid was slightly enlarged and diffusely nodular. The heart was diffusely enlarged. Except for tachycardia there were no electrocardiographic changes. Ecchymoses were scattered over the lower extremities

and there was pitting edema about the ankles. Marked muscular weakness, increase in the tendon reflexes, ankle clonus, and aphonia were present. It was thought that she was too ill for surgery and there was some question whether, judging from the complicated symptomatology and physical findings, all of her difficulties could be attributed to hyperthyroidism. A neurologic diagnosis of amyotrophic lateral sclerosis was considered possible. On January 17 vitamin B therapy in the form of 30 Gm. daily of Yeast-Vitamin Powder (Harris) was begun. On January 24, improvement was noted and by February 16 the patient was very much stronger, appetite was good and gastro-intestinal symptoms, including diarrhea, had subsided. The tongue was normal in appearance. Edema was relieved. Pains in the extremities were no longer complained of, aphonia was completely relieved, and, except for continued muscular weakness and tremor, the neurologic findings were normal. The patient failed to gain in weight, however, and the typical signs of hyperthyroidism continued. The basal metabolic rate remained between  $+40$  and  $+60$  per cent. At this time, through a misunderstanding, vitamin therapy was withdrawn and by March 20 all of the findings originally noted had returned. All forms of standard medical therapy for the treatment of hyperthyroidism were given, including roentgen ray therapy, without improvement in the patient's condition. On April 7, 1934, right lobectomy was performed and on May 18, 1934, the left lobe was removed. Following these procedures the patient's basal metabolic rate became normal and, without further treatment of any kind, she quickly returned to normal in every respect. When last seen on May 21, 1936, she weighed 164 pounds and was entirely normal.

This case is presented to show the increased demand for vitamin B in hyperthyroidism as evidenced by the appearance of the typical clinical manifestations of vitamin B deficiency, which were controlled by administering vitamin B in adequate quantities, even though the basal metabolic rate remained elevated. When the metabolic rate returned to normal the patient remained free of evidences of vitamin B deficiency on an average intake of that substance.



**Case III.**—S. K., thirty years of age, a white male, was admitted to the medical ward on October 1, 1935. The patient had always been a "finicky eater," for the most part eschewing animal foods, but had remained essentially well until September, 1935, when he suffered what appeared to be an attack of acute gastro-enteritis. Diarrhea resisted all local therapy, however, and when admitted, he presented the typical picture of ulcerative colitis. From October to January all standard measures for the treatment of this condition were without success and by this time the patient had developed definite edema of the ankles and serum protein was 3.8 Gm. per cent. At this time the patient suffered an attack of acute appendicitis and at operation a ruptured appendix was removed. Almost immediately following operation he began to vomit, diarrhea increased and became bloody, edema became extensive. A prolonged febrile course ensued and on February 4 it was necessary again to operate for a pelvic abscess. Following this surgical procedure the vomiting became uncontrollable, edema increased still further, the tongue became red, smooth and sore. An erythematous dermatitis appeared on the dorsa of both forearms, he complained of pains in both lower extremities and his vibratory sense, at first impaired, was soon lost in both lower extremities. He appeared to be in a moribund condition. At this time vitamin B therapy was begun in the form of liver extract No. 343 (Lilly), 5 cc. intramuscularly daily; Yeast-Vitamin Powder (Harris), 21 Gm., and an especially prepared wheat embryo extract, 25 cc. (525 Sherman units), by mouth daily. Improvement began in two weeks at which time vomiting was controlled and the tongue became normal in appearance. Gradually the other signs subsided until, at the end of eight weeks edema was gone, serum protein was 4.2 Gm. per cent, neurologic examination was negative and there were no neurologic complaints. Dermatitis had subsided. There had been a gain in weight of 10 pounds and, except for some looseness of the stools, he was apparently normal. All vitamin therapy was withdrawn and on May 24, 1936, he was allowed to return home on his regular diet. He remained well until June when he lost his appetite and gradually all of the symptoms and signs previously noted returned. He was seen in the hospital again in September at which time his

condition was as described in February. Before therapy could be instituted one of the ulcers in the colon perforated and the patient died of general peritonitis.

This case is presented to show that in an individual, whose vitamin intake had apparently been just adequate to meet ordinary requirements, the occurrence of an acute diarrhea, accompanied by decreased absorption from the intestinal tract, was sufficient to precipitate a state of deficiency. This deficiency did not become definite, however, until following surgical procedures which were accompanied by decreased intake of food and by fever. At that time the characteristic evidences of vitamin B deficiency became manifest. Parenteral and oral administration of vitamin B resulted in slow improvement. The patient remained well until vitamin therapy was withdrawn when, probably due to a combination of inadequate vitamin intake and inadequate absorption, the result of permanent damage to the intestine, a state of deficiency again developed. It is, of course, a matter for speculation whether this man could have been kept in good health by continued administration of vitamin supplements but from experience which we have had with subsequent cases of colitis, it would seem wise to continue this form of therapy indefinitely.

**Case IV.**—F. S., sixty-one years of age, a white female, has been seen in the Gastro-Intestinal Section at intervals since 1933. She had complained of vague epigastric discomfort for about fifteen years prior to coming to the Section. For the past six years she had complained of weakness, vertigo, soreness of the tongue and recently of a feeling of numbness and cramps in the calves of the legs at night. She had noticed slight swelling of the ankles in the last few months, dyspnea and a peculiar pallor of the skin. These symptoms, though not incapacitating, made it difficult for her to do her daily work. Blood pressure 112/80, pulse 65, red blood cells 4,600,000, hemoglobin 86 per cent, serum protein 6.8 Gm. per cent. On examination, waxen pallor of her skin was noted and there were several ecchymotic areas scattered over the lower extremities. There was definite edema about the ankles. No abnormalities were detected on examination of the heart. Electrocardiogram was normal except for the bradycardia.

The tongue was red and smooth. Gastric analysis revealed achlorhydria with histamine. Roentgen examination of the gastro-intestinal tract disclosed no abnormalities. Vibration sense was not perceived in the lower extremities. She was first given Yeast-Vitamin Powder (Harris), 30 Gm. daily, in October, 1933. Improvement began in two weeks and at the end of the month she was relieved of the symptoms which had brought her to the hospital. The tongue became normal in appearance, edema disappeared and vibratory sense returned in the lower extremities. The yeast has been continued to the present, with intervals in which it has been withheld always being accompanied by a return of the original symptoms. As long as the yeast is taken in the above dosage the patient is maintained in average good health. There has been no alteration in gastric acidity during the period of observation.

This patient is characteristic of many of her age and sex whom we have encountered with similar symptomatology and who have been relieved by the therapy employed in this instance. In many of these patients achlorhydria has been a finding, although not invariably so.

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### ESSENTIAL PENTOSURIA

To diagnose pentosuria correctly is a matter of practical importance since patients presenting this anomaly are frequently mistreated for diabetes mellitus. Recent studies would indicate that the occurrence of pentosuria may not be as exceedingly rare as it had been formerly presumed. Individuals with pentosuria present no known symptoms by which the existence of this error of metabolism might be suspected, and the recognition of the condition depends entirely upon the response of a given urine to certain appropriate tests. Employing a simple test which contributes to the identification of the pentose, *l*-xyloketose, and which can be easily made in the course of the routine examination of urine, Englewitz and Lasker<sup>1</sup> were enabled in 1933 to add 12 cases of pentosuria to the approximately 100 cases which had been previously reported in the entire literature. Within the past year Lasker, Englewitz and Lasker<sup>2</sup> have extended their studies to include observations on 41 pentosurics. Moreover, these authors report that Blatherwick has discovered 31 additional cases of pentosuria in the analysis of 130,985 specimens of urine submitted to the Metropolitan Life Insurance Company for examination. A recent discovery of pentosuria in a patient and in 3 other members of the patient's family has prompted us to comment briefly upon the studies which have led to the diagnosis of this condition.

#### SUMMARY OF THE HISTORY AND PHYSICAL EXAMINATION OF THE PATIENT

An eight-year-old Jewish girl was admitted to the University Hospital on Dr. J. C. Gitting's service because of burning

on urination and enuresis since infancy. The enuresis was so severe that the act of walking usually resulted in an incontinence of urine.

Physical examination revealed an essentially healthy girl about 20 per cent above her ideal weight. A cystoscopic examination showed a low-grade diffuse inflammation of the bladder mucosa and an abnormally enlarged and thickened internal sphincter. The diagnosis of mild diffuse cystitis of undetermined etiology and a congenital malformation of the internal sphincter was made.

After her admission to the ward it was found that practically every specimen of her urine examined reduced Benedict's solution. The concentrations of blood sugar, obtained after fasting and after the ingestion of glucose, were within the normal limits and the excretion of sugar appeared to be unaltered by changes in the composition of the diet. These findings led to an investigation of the nature of the urinary sugar, which was later identified as the pentose, *l*-xyloketose.

It may be noteworthy that the parents of the patient are first cousins and that one of her brothers is a deaf-mute.

The early literature of pentosuria has been reviewed by Garrod in his excellent monograph on "Inborn Errors of Metabolism."<sup>3</sup> In brief, the discovery of pentosuria came only a few years after the discovery of the existence of sugars of the pentose group. In 1887 Killiani showed that arabinose, the sugar obtained from gum arabic, which had previously been classified as a hexose contained only 5 carbon atoms in its molecule. Shortly afterward it was shown that xylose, the sugar obtained from wood, was also a pentose and that many vegetable structures contained polysaccharides of high molecular weight, known as pentosans, which on hydrolysis yield the aldopentoses, *l*-arabinose and *d*-xylose.

The first case of pentosuria was described by Salkowski and Jastrowitz<sup>4</sup> in 1892. Analyzing the urine of a morphine addict these workers coincidentally found that the urine contained a sugar the osazone of which had a melting point between 157° and 158° C. and was soluble in hot water, in contrast to the osazone obtained from glucose which had a higher melting point and was relatively insoluble in hot water. The crystalline structure of both osazones was similar. The

low melting point of the osazone suggested to these investigators that the sugar present in their patient's urine was a pentose.

As other cases were reported it was soon recognized that two types of pentosuria existed, an alimentary and an essential pentosuria. The alimentary type was found without any associated error of metabolism. Von Jaksch<sup>5</sup> demonstrated that when unfermented fruit juices containing arabinose, such as cider, were ingested in large quantities by certain individuals, the urinary excretion during the following twenty-four hours frequently yielded the pentose, arabinose. On the other hand, in essential pentosuria the excretion of the pentose was unrelated to the composition of the diet and the disorder occurred almost entirely in the Jewish race, and mostly in males.

Essential pentosuria is generally regarded as a harmless and symptomless condition. After reviewing the literature, Margolis<sup>6</sup> pointed out that of the 44 cases reported with adequate clinical histories up to 1929, approximately one fourth suffered from headaches and three fourths were psychoneurotic. Garrod in his studies suggests, however, that racial temperament and the fact that most of the individuals with pentosuria had been under treatment for diabetes might be contributory factors in accounting for psychoneurotic symptoms. There is no reason to believe that the presence of pentosuria decreases the span of life.

In the older literature almost every known pentose has been described as occurring in the urine of pentosurics. However, since Levene and La Forge's<sup>7</sup> studies in 1914 and Hiller's<sup>8</sup> studies in 1917, in almost all of the cases of essential pentosuria thoroughly studied *l*-xyloketose has been the pentose found, although racemic arabinose also has been reported. In alimentary pentosuria the responsible sugar is generally regarded as arabinose.

The source of *l*-xyloketose excreted in the urine is unknown. When xylose is injected into dogs about 65 per cent is excreted unchanged, whereas when *l*-xyloketose is injected only 8 to 14 per cent is excreted unchanged. From these experiments Greenwald<sup>9</sup> concluded that *l*-xyloketose can be metabolized in the body. Moreover, Englewitz and Lasker<sup>1</sup> fed a

pentosuric 5 Gm. of *l*-xyloketose isolated from his own urine and found that the amount of the pentose excreted within the twenty-four hours after the ingestion was only 0.5 Gm. more than the usual excretion. They concluded that an individual with pentosuria can either utilize or destroy *l*-xyloketose when it is administered by mouth.

Chemical theory demands the existence of 8 aldopentoses and their 4 corresponding ketoses (Table 1). Of the 8 aldo-

TABLE 1

## PENTOSES

Aldoses (-CHO)		Ketoses (CO)	
<i>d</i> -ribose (-)	<i>l</i> -ribose (+)	<i>d</i> -riboketose	<i>l</i> -riboketose
<i>d</i> -arabinose (-)	<i>l</i> -arabinose (+)		
<i>d</i> -lyxose (-)	<i>l</i> -lyxose (+)		
<i>d</i> -xylose (+)	<i>l</i> -xylose (-)	<i>d</i> -xyloketose (-)	<i>l</i> -xyloketose (+)

*d* and *l* forms  
related to

*d*-glyceric aldehyde (+)

*l*-glyceric aldehyde (-)

pentoses 7 are known, *l*-xylose apparently having not been isolated. Of the ketopentoses, so far as we are aware, only *l*-xyloketose has been obtained in the pure state. It should be pointed out that the prefixes *d* and *l* given in Table 1 do not indicate the direction of optical rotation but refer to the spatial configuration of the molecule as related to the *d* and *l* forms of glyceric aldehyde.\* In the early literature confusion in terminology exists so that *l*-xyloketose is sometimes referred to as *d*-xyloketose. The signs + and - refer to dextro- and levorotatory properties respectively. Thus, for example, *l*-xyloketose is dextrorotatory.

In Table 2 are given tests by which pentosuria may be differentiated from glycosuria. The pentoses are not ferment-

\* It has been arbitrarily agreed upon to designate sugars with the grouping

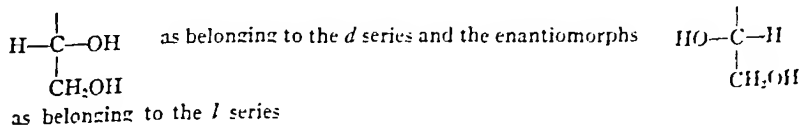




TABLE 2  
DIFFERENTIATION OF PENTOSURIA AND GLYCOSURIA

	Pentosuria.		Glycosuria.
	<i>l</i> -xyloketose.	<i>dl</i> -arabinose.	Glucose.
Fermentation.....	0	0	+
Orcinol HCl (Bial).....	+	+	0
Osazones.....	needles	needles	rosettes; needles
Optical activity.....	dextro	inactive	dextro
M. P. osazones.....	156°-160° C.		210° C.
Reducing bodies:			
(a) Boiling.....	+	+	+
(b) 50° C. for 10 minutes...	+	0	0
(c) after bromination.....	+	0	0
Glucose tolerance.....	normal	normal	diabetic or normal

able. The addition of HCl to pentoses yields furfural; on the addition of orcinol, furfural forms a green-black dye product. This test, known as Bial's dye test is useful as a qualitative test for the presence of pentose although it should be recognized that menthol, turpentine and other organic chemicals may also give the same reaction. The optical properties of the urine in pentosuria have not been reported with any degree of consistency. Most of the reports would suggest that the urine is optically inactive. However, Hiller's studies would indicate that if the urine be concentrated and if *l*-xyloketose be present, the optical rotation is to the right. Racemic arabinose is optically inactive and if present would not contribute to the optical rotation of the urine. The melting point of the purified osazone of *l*-xyloketose is between 156° and 160° C., whereas the melting point of the glucosazone is approximately 210° C. On boiling, both pentoses and hexoses reduce Fehling's or Benedict's solution; however, on heating to 50° C. for ten minutes only *l*-xyloketose will reduce the copper of these solutions. Bromination as described by Hiller may be used to differentiate between the aldose and ketose sugars. The ketoses are capable of reducing Benedict's solution after bromination, whereas the aldoses are not. The glucose tolerance curve is of the normal type in pentosurics; of the diabetic type in glycosurics, excepting in renal diabetes in which the glucose tolerance curve may be normal.

In 1933 Lasker and Englewitz<sup>10</sup> reported a simple procedure which should facilitate the recognition of essential pentosuria in office practice. These workers found that the addition of 1 cc. of urine to 5 cc. of Benedict's qualitative solution gave reduction at 50° C. within ten minutes, provided the urine contained the pentose, *l*-xyloketose, in at least 0.1 per cent concentration. None of the other sugars examined by them gave reduction within this interval of time; the closest was levulose which required twenty minutes at 50° C., and levulose is rarely found in urine. In Table 3 are given data taken from Lasker and Englewitz's studies indicating the periods of time required for the reduction of various sugars which they studied.

The urine of our patient reduced Benedict's solution within ten minutes when heated at 50° C.; was nonfermentable; gave a greenish color when treated with Bial's reagent, and yielded needle-like osazone crystals when treated with phenylhydrazine. Using Hiller's method the same amount of reduction of Benedict's solution was found after bromination of the sugar as before. Furthermore, a purified osazone was prepared which gave a sharp melting point at 158.7° C., thus identifying the sugar as *l*-xyloketose.

TABLE 3

DATA FROM LASKER AND ENGLEWITZ'S STUDIES FOR REDUCTION WITH BENEDICT'S SOLUTION AT 50° C.

Sugar (0.3 per cent).	Minutes.
<i>l</i> -xyloketose	1 5 8
<i>d</i> -fructose	20
<i>l</i> -xylose	43
<i>dl</i> -arabinose	58
glucose	68
lactose	88

In Figs. 67 and 68 are shown the long "needle-like" crystals of the osazone of *l*-xyloketose isolated from the urine of our patient and the "sheaf of wheat" type of gluco-osazone crystals obtained from a glucose solution. In structure the two types of crystals resemble each other.

Since essential pentosuria is known to be a familial con-



Fig. 67.



Fig. 68.

Fig. 67.—Glucosazone crystals.

Fig. 68.—Pentosazone (*l*-xyloketose) crystals isolated from the urine.

dition samples of blood and urine from other members of the patient's family were examined. The results of these analyses are given in Table 4. The analyses would indicate that in this

TABLE 4  
ANALYSES OF URINE AND BLOOD

	Urine.				Blood.
	Benedict's solution, 100° C.	Benedict's solution, 50° C. after 10 min.	Fermentation.	Orcinol HCl reaction.	Fasting sugar, mg./100ml.
Father .....	—	—	0	—	71
Mother .....	+	?	0	?	—
Rose (patient) .....	+	+	0	+	76
Morris .....	+	+	0	+	90
Sol .....	+	+	0	+	96
Julius .....	—	—	0	—	—

family of 6 individuals 3 children and possibly the mother were pentosurics.\*

\* The mother was uncooperative and refused to submit to further studies.

In clinical and insurance practice any individual whose urine reduces Benedict's solution and in whom the concentration of blood sugar is within the normal limits should be suspected of having either pentosuria or renal glycosuria. Support for the diagnosis of the former might be easily obtained by testing the urine for *l*-xyloketose according to the Lasker and Englewitz procedure.

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### TREATMENT OF MENORRHAGIA AND METRORRHAGIA IN THE ADOLESCENT

MENORRHAGIA and metrorrhagia are time-honored terms, the former meaning increase in amount or duration of uterine bleeding or both, at the regular interval; whereas the latter refers to uterine bleeding at times irrespective of the regular rhythm. Hemorrhage, in general, is an abnormal process except in the function of menstruation, when hemorrhage from the uterus occurs normally at relatively regular intervals. It is only when there are abnormalities in the quantity and rhythm of the menstrual flow that uterine hemorrhage takes the aspect of a pathologic process.

Recent advances in research concerning the physiology of menstruation has helped to emphasize the extreme complexity of the normal mechanism. Today menstruation is recognized as an endocrine phenomenon and this added knowledge has illuminated and assisted in the explanation of many problems concerned in its disorders.

In considering causative factors in abnormal uterine bleeding pathology in function as well as pathology in anatomy must be taken in account. Therefore causes are classified as: (1) constitutional, (2) local or organic, and (3) functional. In the adolescent, constitutional and functional causes are the ones of most interest; the constitutional because of their indirect effect upon the endocrine system and the functional because puberty and early adolescence mark a period of relative endocrine instability.

1. Constitutional diseases *per se* are as a rule associated with scanty periods. Amenorrhea is the more common observation. However, irregular and excessive flow does occur and profound anemia becomes a sequel. Excessive uterine bleed-

ing associated with pelvic pain necessitates the ruling out of tuberculosis of the fallopian tubes. Certain blood dyscrasias must be considered because so frequently uterine bleeding is the only outstanding symptom. Chronic thrombocytopenic purpura may manifest itself first in severe menorrhagia. Acute infectious diseases rarely cause uterine bleeding. Influenza is an exception in that it accelerates and aggravates the menstrual flow. Chronic valvular heart disease with its associated passive congestion of the pelvis may at times be a responsible cause. Nervous disorders must not be overlooked in the adolescent. Sudden shocks and severe frights have been known to precipitate profound uterine hemorrhage.

2. **Local or organic disorders** in the generative system are rarely observed as cause of abnormal uterine bleeding in the adolescent. Less frequently are we concerned here with uterine displacements, polyps, myoma, adnexal disorders, carcinoma and ovarian new growths. However, they must all be ruled out, even when studying an adolescent. Granulosa cell carcinoma of the ovary does occur in the young girl and even in children. Carcinoma of the uterus has been found in the immature woman, although it is a very rare finding. Pregnancy and its many disorders with bleeding must be considered.

3. It is with the **functional** causes we are most concerned. Under this classification fall all cases of atypical menstruation in an apparently normal, well young girl. "Functional uterine bleeding," more fittingly called "dysfunctional uterine bleeding," is the term used to refer to those disturbances in uterine bleeding, either menorrhagia or metrorrhagia, which have apparently no definitely demonstrable organic or constitutional conditions as a cause. This form of atypical bleeding is accepted now as due to a disturbance in the hormonal mechanism that controls normal menstruation. This type of bleeding may commence at puberty or may commence after one or several normal periods. Menstrual irregularities are noted as shortened interval, or change in rhythm with intermenstrual spotting of brownish discharge. Very profuse prolonged periods may be the beginning in some cases with only short intervals which may or may not be attended by a constant brown discharge. As a rule, these cases run a more or less mild and chronic course with anemia the outstanding

systemic manifestation. Fortunately, many cases spontaneously adjust themselves. However, others may and do assume a very grave course with profound secondary anemia.

Endocrinopathic evidences are absent in most of the dysfunctional uterine bleeding cases of adolescence. There is little evidence, if any, of hyperthyroidism or hypothyroidism. The girl may be either thin or fat and is usually a very normal feminine type.

In order to understand the rational of the treatment, a brief explanation of the accepted rôles of the endocrines as they influence both normal and abnormal uterine bleeding must be given. The pituitary gland, the ovaries and the uterus are necessary for menstruation. The anterior lobe of the pituitary body produces two known gonadotropic secretions, the follicle stimulating hormone (prolan A) and the luteinizing hormone (prolan B). These secretions act upon the ovaries which produce the estrogenic hormone (follicular hormone, theelin or estrin) and progesterin. The influence of this coordinate function is in turn exerted on the endometrium to bring about the cyclic changes which end in bleeding. Estrin dominates the first half of the cycle and stimulates proliferation of the endometrium. In normal states, under the influence of the luteinizing hormone of the anterior pituitary body, ovulation occurs and the ruptured follicle becomes a corpus luteum. Progesterin, a hormone of the corpus luteum, then takes control of the endometrium and the secretory stage ensues. What actually causes menstrual bleeding is not definitely understood.

Studies by Schroeder<sup>1</sup> and later by others have demonstrated that the ovaries in most dysfunctional uterine bleeding cases show a characteristic finding, namely, absence of corpora lutea and a persistence of unruptured graafian follicles. This is interpreted to mean a persistence of ovarian follicular hormone (estrin, theelin, folliculin) with absence of progesterin or the luteinizing hormone. Persistence of follicular hormone continues the proliferative state of the endometrium without the secretory influence of progesterin. This proliferative state results in a cystic hyperplasia of the endometrium. Bleeding occurs and the endometrium apparently is never completely shed. According to Schroeder this bleeding comes from superficial necrosis, the result of capillary thrombosis. Pankow<sup>2</sup>

and more recently Traut and Kuder<sup>3</sup> and others have demonstrated a lack of conformity to any single type of endometrium in all dysfunctional bleeding cases. Pathologic examinations show in addition to "cystic hyperplasia," "irregular maturation of the endometrium," and "defective shedding." Anspach and Hoffman<sup>4</sup> (1934) confirmed these findings and they were also borne out in a series of cases reported by Macfarlane<sup>5</sup> (1936). Hartman's<sup>6</sup> hypothesis, based upon experiments with monkeys, that bleeding *per se* is due to a special nongonadotropic hormone in the anterior lobe of the hypophysis may be the explanation. Novak<sup>7</sup> likewise agrees that whatever the factor is, it certainly seems in some way bound up with a disturbance in the balance between the two anterior pituitary hormones. An excess of the bleeding factor and a deficiency or absence of the lutein tissue and its hormone appear to go together. Wilson and Kurzrok<sup>8</sup> accept this theory and advance the hypothesis that this bleeding hormone is stimulated by the follicular hormone but inhibited by progesterin and that bleeding ensues when a certain concentration of follicular hormone is reached unless inhibited by progesterin.

All investigators, however, agree that an imbalance exists between the two ovarian hormones and that the ovarian governing principles of the anterior pituitary body play the important rôles and therefore constitute the main factor in the production of this disorder. What external or internal factors affect the pituitary gland to bring about this disorder in the menstrual cycle is not yet proved.

Other glands of internal secretion especially the thyroid have been known to be associated with excessive menstruation. What rôle they play other than an indirect influence is not explained.

**Diagnosis.**—Menorrhagia or metrorrhagia at puberty and during adolescence, although practically always due to disturbance of function, demands a general physical examination and a bimanual examination of the pelvic organs by rectum and abdomen. A blood count, urinalysis and basal metabolism must be done. In this manner rare cases of neoplastic, inflammatory or tuberculous diseases may be eliminated as well as postpregnancy disorders. Aspiration curettage in diagnosis had better be reserved for the mature woman.



**Treatment.**—*Constitutional and Tonic.*—If pelvic pathology or constitutional disease is found the treatment is directed toward the elimination of the pathologic condition. But in the absence of organic lesions treatment in the young should consist of all general measures for upbuilding the health. Time-honored employment of rest, hygienic measures, tonic treatment and iron administration between bleeding periods, must be employed. Oxytocic drugs, ergot and pituitrin, will temporarily diminish the bleeding but since there is no evidence to show that failure of muscular contractibility is a major cause, their usage is palliative. Attempts at increasing the coagulability of the blood may be accomplished by administration of large doses of calcium by mouth, intravenously or intramuscularly. Severe cases of excessive bleeding even necessitate blood transfusions, one or more. Blood of a pregnant donor has been advised. In adolescent bleeding cases, irradiation of the spleen has been effective in diminishing the bleeding and so temporarily bringing relief. Water moccasin venom has received attention in the treatment of dysfunctional uterine bleeding. This form of therapy attempts to diminish the permeability of the blood vessel walls. Peck and Goldberger<sup>9</sup> and Frank<sup>10</sup> report satisfactory results, but results at best are temporary. As said before, many cases of mild form correct themselves spontaneously or after certain constitutional and tonic aids. Others require the most painstaking study and treatment.

*Endocrine Therapy.*—Endocrine therapy in dysfunctional uterine bleeding cases consists in the administration of extracts of the corpus luteum, extracts made from pregnancy urine and placental extracts, and extracts of the anterior pituitary body. Since lack of progestin or inadequate amount is responsible in most cases, the treatment would seem to be directly substitutive. Potent extracts of the corpus luteum in sufficient dosage has not become commercially available because of the limited source of supply. Extracts which have gonadotropic effects have been made from the urine of pregnant women and from placenta. But because they appear not to be identical to the extracts of the anterior pituitary body, though having similar effects, they are called "anterior pituitary-like hormones." The source of supply is abundant, hence these ex-

tracts offer the best method of stimulative treatment. Antuitrin S (Parke, Davis), anterior pituitary-like hormone A. P. L. (Collip), follutein (Squibb), and other commercial preparations are on the market at the present time containing the gonadotropic fraction. Any one of these preparations have given good results when used in sufficiently large doses. Two hundred to 500 rat units must be given daily to bleeding cases. The dose is diminished as the bleeding ceases and the interval increases. Two hundred rat units are given twice a week after bleeding stops for an indefinite number of weeks, until the bleeding is controlled. Surprising results have been achieved with this form of therapy. Occasionally a period of prolonged amenorrhea may ensue, but this is not objectionable, especially if there exists a severe anemia. This permits time for the rebuilding of the blood and frequently the endocrine mechanism reestablishes an equilibrium. The exact method by which this anterior pituitary-like hormone controls dysfunctional uterine bleeding has not been definitely established. The control may be inhibitory on the bleeding factor since experiments have shown absence of effect on the endometrium. Anterior pituitary extracts have offered good results but not so effectively as the extracts of pregnancy urine and placental tissue.

One must not forget the coordinating influence of the other glands of internal secretion. The thyroid especially must be considered in cases with low basal metabolic rate and hypothyroid manifestations. Thyroid therapy in some cases has been attended by excellent results. The administration of insulin has produced favorable results in shortening the duration of bleeding in juveniles. Most of the good results as reported by Klaften,<sup>11</sup> however, were obtained in that group of women who had a hereditary history of diabetes or in those who later developed diabetes and in the underweight group.

*Surgical Treatment.*—Failure of endocrine therapy in the past and possibly impatience on the part of the patient or her family, has led to other more radical procedures. Persistence in treatment on the part of the physician and confidence in the physician on the part of the patient are two very necessary attributes for success in the treatment of adolescent uterine dysfunctional bleeding. The time-honored curettage which

was formerly done in those intractable cases has now come into its own probably more for its diagnostic than therapeutic usage. However, the fact that some cases are followed by recovery, places the procedure in the category of treatment as well. Occasionally repeated curettements are found necessary. Certainly in light of our present knowledge of the physiology the removal of the bleeding surface can only afford temporary relief. In adolescent bleeding curettage should be especially limited because of the psychic effect on the patient.

Novak<sup>12</sup> so highly regards the endometrium as the registering board of the two ovarian hormones that he emphasizes the importance of the microscopic study of the endometrium in all cases of menstrual disorder and considers more can be obtained by aspiration curettage concerning ovarian activity than from blood and urine hormone studies. This procedure, however, though very simple and can be done in the office without anesthesia, is hardly desirable except in intractable cases in the young adolescents.

Radical surgery in the young woman can only be considered in very grave cases. Resection of both ovaries, or removal of one ovary in order to diminish the amount of persisting follicular influence is attended by only temporary success which hardly justifies the procedure. Other more radical operations as bilateral oophorectomy, supravaginal hysterectomy or even fundectomy should have no place in the treatment of juvenile uterine bleeding except as a last resort in that occasional grave case.

*Radium Therapy.*—Because of the serious effect upon the child-bearing function, treatment by radium should be deferred. Small doses of radium—300 to 800 mg. hours of radium—will temporarily check the bleeding and may be used when endocrine therapy, curettage and constitutional aids do not control the bleeding. This will give a temporary cessation and the periods will return, at times normally, at other times atypically. Radium therapy may have to be repeated.

*x-Ray Therapy.*—x-Ray over the ovaries should be reserved as treatment for the woman near her menopause and therefore has no place in the treatment of the adolescent. Irradiation of the pituitary gland has been reported as giving immediate relief. Small doses of x-ray are said to bring about

increased pituitary activity with stimulation of the ovaries to normal function. This method of treatment has not, however, received universal accord and does present a method of treatment attended by too many dangerous possibilities to warrant its use.

To summarize the treatment of menorrhagia and metrorrhagia in the adolescent:

1. Constitutional and tonic aids chiefly by drugs directed toward the anemia, transfusion of whole or citrated blood in severe cases, and oxytocic drugs to control the bleeding.

2. Administration of extracts of pregnancy urine in large doses.

3. Curettage, even repeatedly, in intractable cases.

4. Radium in small dosages in those grave bleeding cases which will not respond to any other form of therapy.

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*Baltimore Number*

# THE MEDICAL CLINICS OF NORTH AMERICA

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## SYMPOSIUM ON DISEASES OF CHILDREN

The following clinics are included in this Symposium:

C. Loring Joslin: SOME CAUSES OF MALNUTRITION IN INFANCY.

William S. Love, Jr.: THE DIAGNOSIS OF HEART DISEASE IN CHILDREN.

James G. Arnold, Jr.: THE DIAGNOSIS AND TREATMENT OF OTITIC MENINGITIS.

Edward A. Looper: INFECTION OF THE NASAL ACCESSORY SINUSES IN CHILDREN.

H. Whitman Newell: THE EFFECT OF HEAD INJURY ON THE BEHAVIOR AND PERSONALITY OF CHILDREN: A STUDY OF 20 CASES.

Cyrus F. Horine and George S. Baker: ACUTE EMPYEMA IN CHILDREN: DURATION OF ILLNESS PRIOR TO TREATMENT A FACTOR IN MORTALITY RATE.

J. Edmund Bradley: DIAGNOSIS OF THE CAUSES OF LOW-GRADE ABDOMINAL PAIN IN CHILDREN.

T. Campbell Goodwin: THE TREATMENT OF ACUTE NEPHRITIS AND ITS COMPLICATIONS IN CHILDHOOD.

Leon Freedom: PROGRESSIVE BIRTH PALSIES.

Harry M. Robinson: TREATMENT OF SYPHILIS IN INFANTS.



## CLINIC OF DR. C. LORING JOSLIN

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### SOME CAUSES OF MALNUTRITION IN INFANCY

THIS presentation will offer some concepts concerning the possible causes of an infant failing to make a progressive or normal gain in weight during the first year of life. Cases illustrating the more frequent causes of malnutrition in infancy with results of treatment will be presented. No attempt will be made to discuss malnutrition in the preschool or older child.

Malnutrition is all too common in pediatric practice. In the dispensary patient, it is frequently a result of the present economic distress because the parents have been unable to purchase sufficient food for normal growth and health. In private practice, the undernourished child frequently presents himself, not as an economic problem, but as a diagnostic and therapeutic difficulty. Malnutrition in the private patient who has freedom from economic stress may be due to one of many causes, or to a combination of several. The etiology is not always clear and may require rather lengthy clinical and laboratory studies before it is apparent. The average medical student does not see as many cases of extreme malnutrition (marasmus) today as were seen twenty years ago. This is due to simplified methods of infant feeding and a better knowledge of underlying conditions. The student is likewise taught that the growth and development of the infant are his direct responsibilities. He soon recognizes that the baby ordinarily will gain if the mother follows the physician's directions and if the child does not present any congenital abnormality. If the baby does not gain on an adequate diet, then there is an error in judgment as regards the particular infant in question. Uncomplicated malnutrition is regrettable be-

cause it is a preventable disorder easily controlled by modifying the diet to suit the digestive characteristics of the individual infant. When other factors enter into the picture, an under-nourished infant may well represent a difficult problem.

A good general outline of the causes of malnutrition is a modification of one offered by Wright, as follows:

#### FAILURE TO GAIN WEIGHT

I. Constitutional or organic	{	Congenital	{ Anatomical, <i>e. g.</i> , amyotonia congenita. Congenital heart disease. Defective cerebral development. Various other congenital anomalies.
		Acquired	{ Intracranial hemorrhage. Physiological, <i>e. g.</i> , endocrine disorders.
II. Infection. . . .	{	Parenteral	{ <i>e. g.</i> , otitis media, mastoiditis, pyelitis, tuberculosis, syphilis.
		Enteral	{ <i>e. g.</i> , diarrheal diseases.
III. Food. . . . .	{	Quantity	{ Insufficient calories or too many calories.
		Quality	{ Incorrect formula—fat, protein, carbohydrate, salts, iron, vitamins, etc.
IV. Environment.	{	Home.	
		Outside.	

**Congenital Anomalies.**—*Amyotonia congenita* is among the organic causes of congenital origin. It is rare, but, when it does occur, demands accurate diagnosis because upon this depends prognosis. The disease is thought by some to be a muscular dystrophy, of the Werdnig-Hoffmann type, while others call attention to transitional forms, which possibly connect it with spinal muscular atrophy. The exact etiology is unknown. The chief symptoms concern the muscles, those of the lower extremities being so weak the infant is unable to move its legs. The upper extremities are usually moved, but feebly so; the intercostal muscles are usually involved, while the diaphragm and muscles supplied by the cranial nerves escape. The reflexes are diminished or absent. Various degrees of amyotonia occur, depending on the stage at which the disease is first seen. It either remains stationary or progresses very slowly and the child usually dies of intercurrent infection. Treatment is of no avail. The following case illustrates this condition:



6/14/28. (A.W.)	Age: four months.
Complaint:	Failure to grow and develop.
Family History:	One child living and well. One infant was recorded to have died as a result of "wasting disease" at six weeks of age.
Past History:	Natural birth. Birth weight: 7 pounds.
Present Illness:	Weak and feeble since birth. Weak cry. Has not gained since birth. Stools normal. No vomiting. Feedings: breast-fed for several weeks. Has also been fed modified cow's milk and condensed milk.
Physical Examination:	Lack of development of muscles of entire body, especially of lower extremities (flaccid paralysis). Muscles soft, flabby and general atonic condition. Knee jerks present. No impairment of sensation. Feeble respiratory movements.
Diagnosis:	Amyotonia congenita.

*Congenital heart disease*, in which there is cyanosis, with clubbing of the fingers and toes, is likely to be accompanied by a general malnutrition. The physical examination along with these symptoms should enable the physician to make the diagnosis and to account for the malnutrition on this basis. It is well to remember that frequently congenital anomalies are multiple and others should be searched for.

*Congenital cerebral developmental defects* are also among the causative factors of malnutrition in infancy. These children may apparently do well for a while and then cease to develop normally. In other cases the infant is retarded from the beginning. The disorders may be classified as congenital cerebral diplegias, paraplegias, or hemiplegias. They result in the birth palsies, of which the spastic diplegias are most common. These children rarely are able to stand, walk or talk; their extremities are held spastic and the lower extremities are usually crossed. They are mentally retarded and show little signs of intelligence. As feeding problems they are discouraging since they take little interest in food, especially solid food, so that feedings must be forced upon them. The prognosis at best is poor in these cases and they usually succumb to intercurrent infections. Clinically they are likely to be confused with the picture of intracranial hemorrhage. The differential diagnosis depends largely upon an examination of the spinal fluid, which shows evidence of either fresh bleeding or old bleeding, in the event of hemorrhage, and the absence

of blood and its products in the palsies. In the later months, the tape measure may give evidence of cerebral disorder and occasionally a microcephalic is diagnosed by this simple method. It is important to diagnose the condition, because it is our experience that the mothers of these children are frequently unaware of the nature of the disorder and go from physician to physician in an attempt to rear a normal child, without realizing that their child will never be normal.

**Acquired Defects.**—*Intracranial hemorrhage* has not only recently been recognized as the most frequent cause of death in the newly born, but it may be the cause of an infant failing to gain normally. One of the more common symptoms in the less severe cases of intracranial hemorrhage, is failure to nurse properly and to make a satisfactory weight gain. Fortunately, when there is only moderate intracranial bleeding at birth, the condition clears up spontaneously and the infant will make a normal gain. Frequently, though, this is not the case and it is later observed that the infant is underweight and is not developing normally. Vomiting may result from increased intracranial pressure as a result of intracranial hemorrhage at birth and thus interfere with the nutrition of the child. Vomiting is not a common nor a characteristic symptom of intracranial hemorrhage, but occasionally occurs. The symptoms one is usually able to elicit, suggesting intracranial hemorrhage as a cause of failure to progress normally, are rigidity of neck muscles (intermittent), adductor spasm of lower extremities, spasticity of upper and lower extremities, and attacks of cyanosis.

The following case illustrates the influence intracranial hemorrhage may have upon the weight gain of an infant.

2/18/34. (L.J.N.) Age: two months.

Complaint:	Not gaining. Vomiting
Family History:	Negative.
Past History:	Low forceps delivery. Birth weight, 8 pounds 8 ounces. Formula: modified cow's milk.
Present Illness:	Has not gained since birth. Vomiting since four weeks of age. Change of formulas has no effect upon weight gain or vomiting
Physical Examination	Slight rigidity of neck and spasticity of extremities, especially marked if infant is excited or cries. Adductor spasm of lower extremities. Marked malnutrition

Diagnosis: Intracranial hemorrhage at birth. Vomiting and malnutrition, secondary to increased intracranial pressure, resulting from hemorrhage.

Treatment: Lumbar punctures.

Figure 69 shows graphically the weight gain of this infant before and after institution of treatment.

**Endocrines.**—The endocrines play an important part in the growth and development of the infant. In most cases, an endocrine imbalance is clinically manifested by a faulty growth.

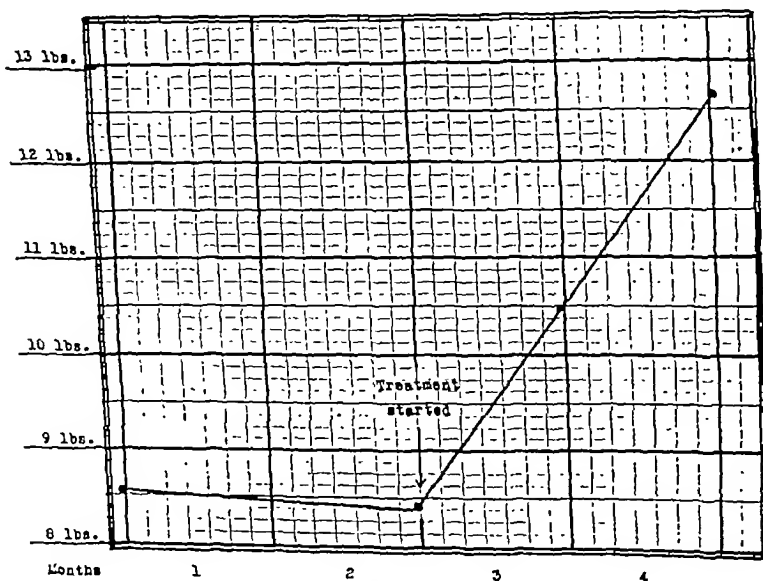


Fig. 69.

*Note.*—Infant gained immediately after first lumbar puncture, which was repeated until pressure symptoms disappeared.

Perhaps the most classical example of this is seen in the cretin, who represents an infant with a deficient secretion or absence of thyroid hormone. These children are short, have coarse features, dry skin, broad nose, frequently a protruding tongue, and show a general lack of development both mentally and physically. The important differential diagnosis is between the cretin and the mongolian idiot. In clear-cut cases there is little difficulty encountered, whereas in others a very careful examination may be necessary. The roentgenographic studies

of the centers of ossification along with growth age and mental age are of great value in orienting oneself as to the status of the child. It is important to remember that large doses of thyroid extract are sometimes necessary to achieve the best results, doses which may bring about a state of temporary hyperthyroidism.

The pituitary is intimately connected with the various types of dwarfs. Disorders of the pineal gland and the thymus gland are not clear as yet. A diagnostic difficulty is frequently encountered where there is a pluriglandular dysfunction.

**Parenteral Infections.**—These are frequent causes of an infant not making the normal gain in weight. Some children are much more susceptible to recurring infections than others, and with each recurring infection the child is retarded in its nutritional gain, until a very definite state of malnutrition exists. *Otitis media* is one of the most frequent of the parenteral infections interfering with nutrition, not infrequently causing a diarrhea with weight loss. *Mastoiditis*, secondary to otitis media, sometimes interferes with nutrition. It is not the usual mastoiditis to which I wish to call attention, but the so-called "hidden mastoiditis," in which there may be no local symptoms, such as swelling or tenderness over the mastoid. Otoscopic examination of the ear likewise does not reveal any appreciable involvement of the tympanic membrane, the diagnosis being based upon the clinical picture as a whole. These cases fortunately are not frequent, but do occur. The onset is usually sudden, with a diarrhea, which persists in spite of all forms of treatment. The infant becomes rapidly dehydrated, toxic, loses weight until it is merely skin and bones. Death always follows unless the correct diagnosis is made and the mastoid is opened and drained. The condition is illustrated by the following case:

10/20 31. (C.T.) Age: five months.

Complaint: Diarrhea, loss of weight.

Family History: Negative.

Past History: Negative. Developed normally until four months of age.

Present Illness: At four months infant developed diarrhea, which has persisted until the present. During the past three weeks the infant has been treated in the hospital and

the diarrhea has become progressively worse in spite of all treatment, averaging from 10 to 15 stools per day. There was a weight loss of several pounds before entering hospital and this loss of weight has continued.

Physical Examination: Extreme malnutrition, dehydration and toxicity. No local evidence of mastoid involvement. Tympanic membrane of right ear shows slight congestion around the circumference; the drum is otherwise negative. Stool cultures, blood, etc., negative.

Diagnosis: Mastoiditis. Diarrhea and malnutrition secondary to a hidden mastoid infection.

Figure 70 shows weight record of this case while in the hospital.

*Pyelitis* is another cause of malnutrition, especially in the female infant, although it may occur in the male as well. These infants are handicapped in their development, they are frequently anemic in appearance and fail to gain because of an active infection in the kidney. Recognition of the cause of the failure to gain depends on completeness of urinary studies. Frequently the diagnosis is missed because only one urinary specimen has been examined, and that at a time when the patient is not eliminating pus in the urine. Anomalies of the genito-urinary tract are often a source of chronic infection and result in malnutrition. These may be so well masked that only necropsy discloses them, as for example in the case of aberrant ureter with infection.

*Tuberculosis* as such is not a common cause of malnutrition in infancy. Here diagnosis does not depend upon physical examination alone, but on tuberculin tests and x-ray findings. The diagnosis should be made when the infant is still well nourished, rather than later, when a state of malnutrition exists, if treatment is going to be effective.

*Syphilis* is another cause of faulty development and failure to grow properly. These cases are pathetic when the condition is marked at birth. The picture is a familiar one and I should only like to call attention to the importance of treating the mother during pregnancy, thus giving prophylactic treatment rather than curative. Attention is also called to the fact that a negative Wassermann during the first few months of life does not rule out congenital lues.

**Enteral Infections.**—The *diarrheal diseases*, while still a problem during the summer months, are not the frequent causes

Form 143-24-544

## UNIVERSITY HOSPITAL

## WEIGHT CHART

Chart #2

NAME G.T. DATE October 20, 1931 WARD C No. 75077 AGE 5 mos.

DAY OF MONTH	DAY IN HOSPITAL	AGE IN MONTHS	AMOUNT OF FOOD
October 20	1	5	15
October 21	2	5	15
October 22	3	5	15
October 23	4	5	15
October 24	5	5	15
October 25	6	5	15
October 26	7	5	15
October 27	8	5	15
October 28	9	5	15
October 29	10	5	15
October 30	11	5	15
November 1	12	5	15
November 2	13	5	15
November 3	14	5	15
November 4	15	5	15
November 5	16	5	15
November 6	17	5	15
November 7	18	5	15
November 8	19	5	15
November 9	20	5	15
November 10	21	5	15
November 11	22	5	15
November 12	23	5	15
November 13	24	5	15
November 14	25	5	15
November 15	26	5	15
November 16	27	5	15
November 17	28	5	15
November 18	29	5	15
November 19	30	5	15
November 20	31	5	15
November 21	32	5	15
November 22	33	5	15
November 23	34	5	15
November 24	35	5	15
November 25	36	5	15
November 26	37	5	15
November 27	38	5	15
November 28	39	5	15
November 29	40	5	15
November 30	41	5	15
December 1	42	5	15
December 2	43	5	15
December 3	44	5	15
December 4	45	5	15
December 5	46	5	15
December 6	47	5	15
December 7	48	5	15
December 8	49	5	15
December 9	50	5	15
December 10	51	5	15
December 11	52	5	15
December 12	53	5	15
December 13	54	5	15
December 14	55	5	15
December 15	56	5	15
December 16	57	5	15
December 17	58	5	15
December 18	59	5	15
December 19	60	5	15
December 20	61	5	15
December 21	62	5	15
December 22	63	5	15
December 23	64	5	15
December 24	65	5	15
December 25	66	5	15
December 26	67	5	15
December 27	68	5	15
December 28	69	5	15
December 29	70	5	15
December 30	71	5	15
December 31	72	5	15

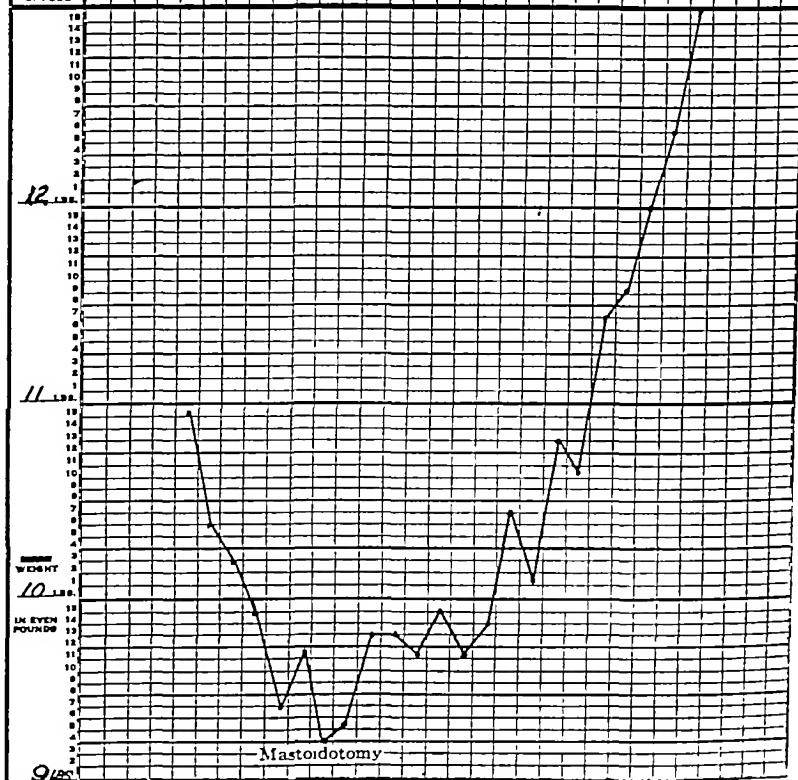


Fig. 70.

*Note.*—There was a loss in weight of 2 pounds after admission to the hospital, which occurred before the mastoid was drained. Following the mastoidectomy the diarrhea immediately ceased, the weight loss was checked, the infant gained slowly for a time and then made an uninterrupted progress to normal weight and health.

of extreme malnutrition as in the past. During the past two years we have been able to carry seventy-five per cent of

our cases of diarrhea and dysentery through their illness without any loss in weight, and when the average of all cases has been taken, there has been a slight gain in weight during the attack of diarrhea. This is quite a contrast to the loss of weight we formerly saw. Many infants fail to make their normal gain in weight during infancy because of recurring attacks of diarrhea. These repeated attacks may be due to intolerance to some one ingredient of the diet, such as too much fat, or carbohydrate, or to too large a quantity per feeding. Recurring parenteral infections may produce the same clinical picture. Of the enteral infections dysentery is the most common, and not infrequently occurs unrecognized, because of the absence of macroscopic blood in the stools.

In the prevention of weight loss from diarrheal diseases, the addition to the diet of the fully ripe banana, or the dehydrated banana powder has proved most effective.

*Typhoid fever* likewise is no longer the producer of such a state of extreme malnutrition as we used to see because of improved methods of feeding these cases.

**Quantity of Food.**—The quantity of food fed to an infant has an obvious effect on his general state of well-being. If he is not getting sufficient calories to supply his maintenance requirements along with his growth requirements, he will not gain. Likewise many infants will not gain if given too much food. There has been a strong tendency during recent years to allow the child to decide for himself the question of how much food he should have. This may be a satisfactory method for some infants, but for others it is not a safe guide. Many an infant who is getting too much food, having colic, and crying frequently will take eagerly an increase in the formula, when what the infant needs is less food. According to my experience, the greatest difficulty the physician has today is in estimating the total caloric requirement of the individual infant. Before the introduction of simplified infant feeding (whole milk modifications) one would see many infants failing to gain because of the quality of the food—but now this has changed, and many infants are seen failing to make an optimum gain because the total caloric intake is not properly adjusted to the individual infant. Those infants failing to gain because of too much food may have recurring attacks of

diarrhea and vomiting, or the infant may be simply refusing part of its feedings. It is well to remember, that there is a maximal point at which an infant will gain, a minimal point, and an optimal point. Many infants are seen suffering from a moderate degree of malnutrition, because such infants are having to subsist on the maximal or minimal number of calories and are not receiving the optimal number upon which they would gain best.

The following case will illustrate the importance of the total caloric intake in relation to the infant's weight gain.

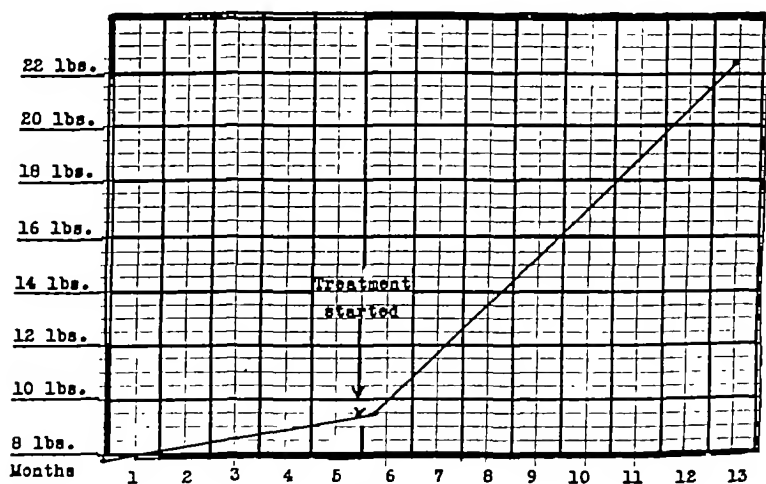


Fig. 71.

*Note.*—In the above chart it will be seen that the infant, although given various formulas and different types of food, made little gain in weight for six months. When the total caloric intake was adjusted to meet the requirements of the infant, there was an immediate and continued weight gain.

11/21/30. (L.H.B.) Age: six months.

Complaint: Not gaining.

Family History: Negative.

Past History: Birth weight, 7 pounds 12 ounces Feeding: breast two months, modified cow's milk, goat's milk, pre-digested milk, condensed milk, cow's milk.

Present Illness: Has gained only 1½ pounds in six months. Vomiting at irregular intervals. Constipated. Present formula: milk, 15 ounces; water, 15 ounces; sugar, 2 table-spoonfuls (42 calories per pound)

Physical Examination: Negative, except for marked degree of undernutrition

Diagnosis: Malnutrition, extreme Feeding, regulation of



Treatment: Formula adjusted to caloric requirements of infant. Milk increased to 18 ounces, sugar to 3 tablespoonfuls (57 calories per pound). No other change was made in the care and feeding of the infant. Formula later increased as baby gained.

**Quality of Food.**—Some infants may receive an adequate quantity of food for proper gain in weight, but have difficulty in gaining because the quality is not suitable.

Premature babies present a special problem, inasmuch as such infants are born with sufficient reserves of iron and other accessory factors to take care of only the immediate needs. The rate of growth is relatively rapid and the premature infant quickly outstrips his reserves so that he is in danger of being undernourished unless the need for the accessories is met. The normal infant tends to grow at a rate commensurate with his natal reserves until the second month is reached. At this time growth has progressed to a point where the stores are not sufficient, and the child has what has been termed a physiologic anemia. Usually the child makes a physiologic adjustment to the situation, and after a variable period, depending on the individual, resumes normal growth.

There are many factors entering into the maintenance of normal nutrition, and it would appear that our concept of normal nutrition is changing. Certainly it is clear that improved nutrition may be obtained for many infants and children, who are generally considered to be in a normal state of health, by the addition of certain vitamins and minerals to their regular diet.

Various degrees of undernutrition, especially nutritional anemias, are produced by a deficiency in the diet, or a lack of balance of certain minerals, such as iron, calcium, phosphorus, and perhaps copper. It has been shown that a preponderance of one mineral may interfere with the utilization of another. From the biochemical standpoint, there are such problems as the secretions of the various ferments that aid in digestion. For example, the amount of hydrochloric acid secreted in the stomach may have an important part in the mechanism of digestion and nutrition.

Our knowledge concerning the vitamins has been greatly increased during recent years, yet our information is still in-

complete. The clinical picture produced by a deficiency of vitamins C and D in the diet is a familiar one to all. The picture of an inadequate amount of vitamins A, B and G is not so clear, yet they are necessary vitamins, and perhaps more important than we have thought. This is shown graph-

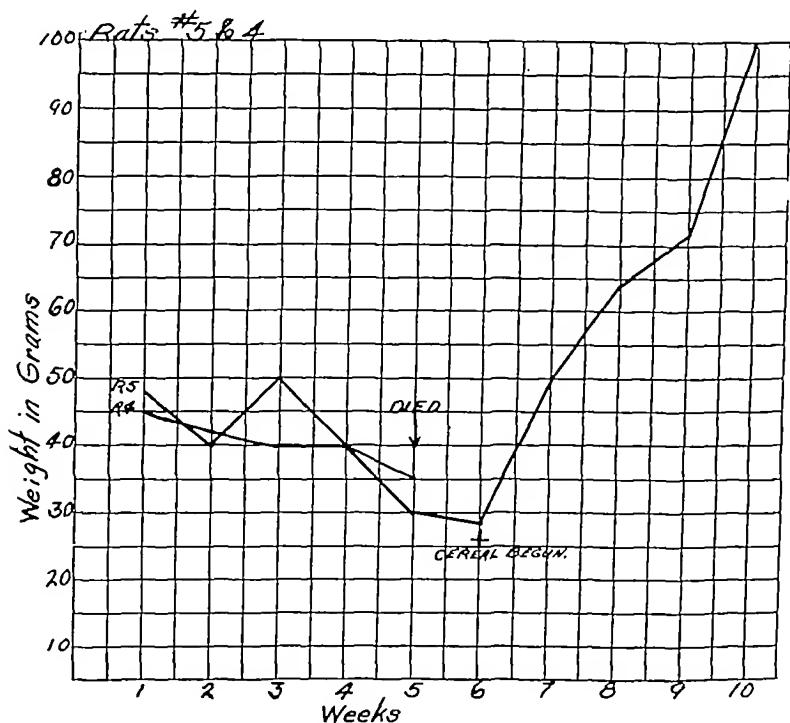


Fig. 72.—Effect of vitamin B complex upon growth of rats.

*Note.*—Vitamin B-free diet was fed for six weeks to 2 rats. Rat 4 died; rat 5 shows progressive loss of weight until vitamin B was added to the diet at six weeks, then follows a progressive gain in weight. It will be seen that without the vitamin B complex in the diet, the rats lose appetite and weight, and soon die. When the vitamin B complex is added to the diet, normal nutrition is rapidly regained, as shown by this chart.

ically in Fig. 72, in which there is given the weight curve of two rats on a vitamin B-free diet for a period of six weeks, after which time the vitamin B complex is added to the diet in the form of a special cereal mixture.

It is also interesting to note that improved nutrition may be obtained by including additional vitamin B and perhaps

minerals in the regular diet of many infants. This is shown in Fig. 73, where a cereal<sup>1</sup> mixture rich in vitamin B and minerals was substituted for the regular cereal being given a group of infants in an orphanage, no other change being made in the diet or routine care. The group receiving the cereal, enriched with vitamins and minerals, had an increased rate of gain in weight and growth as compared to the control group.

The individual tolerance of fat, protein, and carbohydrate should be considered in the feeding of infants who are not making normal progress. Carbohydrate intolerance is not frequent, and protein intolerance causes little trouble, except from an allergic standpoint, as in eczema. If this condition develops early in life the infant's nutrition and growth are temporarily interfered with. Fat intolerance is quite frequent;

*Effect of Special Cereal on Growth of 20 Infants*

	<i>Height in inches</i>			<i>Weight in pounds</i>		
	<i>Initial</i>	<i>After 2 mos.</i>	<i>Gain in inches</i>	<i>Initial</i>	<i>After 2 mos.</i>	<i>Gain in pounds</i>
<i>Control Group</i>	32.1/4	33 1/4	1.0	26.1	27.6	1.5
<i>Special Cereal</i>	30	31.5	1.5	22.13	24.14	2.0

*Special Cereal rich in Vitamin B and minerals*

Fig. 73.

it may be recognized by vomiting, crying from colic, frequent stools, or constipation. The effect of fat intolerance upon nutrition is shown by the following case:

1/12/34. (R.D.G.) Age: five weeks.  
 Complaint: Crying. Not gaining.  
 Family History: Negative.  
 Past History: Natural birth; birth weight, 9 pounds 9 ounces.  
 Present Illness: Crying and has not gained since birth.  
 Physical Examination: Negative, stools frequent and contain large number of fat curds.  
 Diagnosis: Colic. Fat intolerance.  
 Treatment: Fat-free milk.

The bacteriologic flora of the intestinal tract has recently received considerable attention and may at times have a re-

<sup>1</sup> Cerevim.

tarding effect upon nutrition. These cases are frequently diagnosed as chronic intestinal indigestion, and there may be a relationship with celiac disease. The part that the intestinal flora plays in some conditions is not as yet entirely clear, and needs further study.

**Environment.**—The surroundings in which the baby is placed frequently have an important bearing upon its nutrition and general health. The nervous mother, for example,

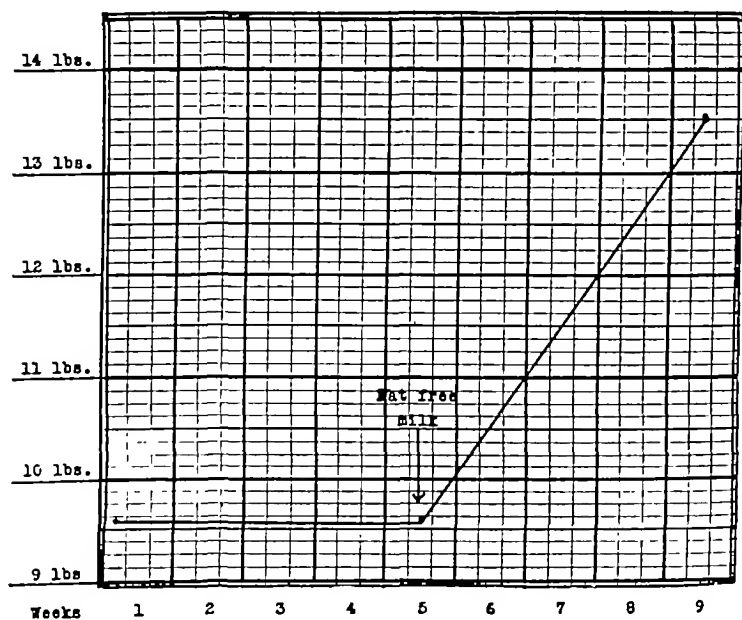


Fig. 74.

*Note.*—There was a gain in weight as soon as fat-free milk was given infant, crying also immediately ceased.

usually leaves her mark upon the baby so that the infant is overexcitable, unable to relax, and generally underweight. Needless to say, the environment outside of the home, as well as within, has an important bearing on the health of the child. Pure fresh air is a prime requisite in the life of every infant. When an infant is deprived of an adequate amount of sunshine its nutrition suffers. During the winter months it is frequently advantageous to compensate for this lack by exposure to the ultraviolet light. It is important that a pains-

taking investigation be made into the environmental factors in every case of failure to gain weight during infancy.

**Summary.**—Little emphasis has been placed upon the treatment of undernutrition in infancy, but an attempt has been made to stress the importance of making a diagnosis as to the cause of the undernutrition. Without a correct diagnosis the treatment may not only be difficult, but may prove costly because the fundamental cause is untouched. Malnutrition in infancy (except in cases of congenital abnormalities) is a preventable condition and should be treated from a prophylactic, rather than from a curative standpoint.



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### THE DIAGNOSIS OF HEART DISEASE IN CHILDREN

IN considering this title it becomes obvious that no adequate discussion of all of its phases could be encompassed in a paper of this scope. I shall therefore limit myself to those conditions in which difficulties of diagnosis most commonly exist, and which are fairly frequent in occurrence.

#### CONGENITAL HEART DISEASE

Maude E. Abbott has rendered a great service by giving us a clinical classification of congenital heart disease which is simple and descriptively to the point. This classification is based upon the presence or absence of cyanosis. While cyanosis may be met with in many conditions, severe cyanosis recurring or constantly present in children is almost always due to congenital heart disease, unless other cause be more or less obvious. The cyanosis of congenital disease of the heart is due to a shunt from the venous to the arterial circuit. It is important to emphasize that the direction of the shunt must be venous-arterial, for only if the shunt is in this direction will the amount of reduced hemoglobin in the arterial blood be sufficient to cause cyanosis. Arteriovenous shunts do not lead to cyanosis unless eventually the direction of flow be reversed by heart failure or other complicating factors; then cyanosis occurs.

We may clinically divide congenital heart lesions into:

1. Those in which no shunt is present—the acyanotic group.
2. Those in which an arteriovenous shunt exists—the potentially cyanotic group.

3. Those in which the shunt is venous-arterial—the cyanotic group.

The variety of lesions which may occur under any of these headings except the second is too great to permit of complete discussion. Only those encountered with some frequency, and permitting of clinical diagnosis, are here described.

#### THE ACYANOTIC GROUP

**Dextrocardia.**—Mirror image dextrocardia with complete situs inversus of the viscera produces no symptoms, and in no way handicaps the patient. The apex of the heart lies to



Fig. 75.—Teleoroentgenogram of heart, mirror image dextrocardia with situs inversus. Note absence of hypertrophy, gas bubble in stomach on right liver on left.

the right and other viscera are transposed. Figures 75 and 76 show the roentgenogram and electrocardiogram of such a case. The electrocardiograms obtained from such cases are typical and are explained in the legend of Fig. 76.



Dextrocardia with partial situs inversus or isolated dextrocardia is usually associated with complex cardiac defects defying complete clinical diagnosis and is usually to be placed in the cyanotic group. Figure 77 presents the x-ray of such a case, a cyanotic infant showing at autopsy isolated dextrocardia, transposition of the aorta and pulmonic artery, a large defect of the interventricular septum, and pulmonic stenosis.

**Coarctation of the Aorta.**—This condition may occur as

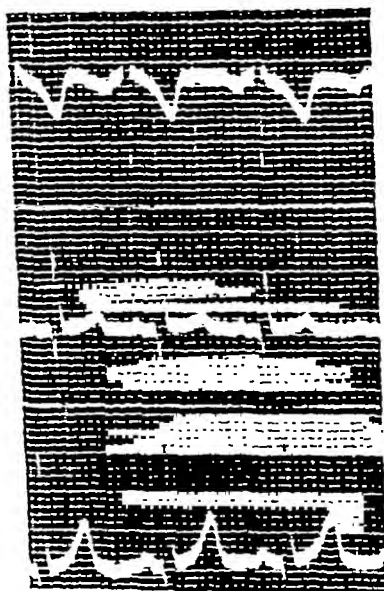


Fig. 76.—Electrocardiogram from same patient shown in Fig. 75. All waves in Lead 1 are *negative*, Lead 2 records what would usually be Lead 3, and Lead 3 records what would be Lead 2. These findings occur because of the altered position of the heart in relation to the leads. There is no axis deviation

a part of complex anomalies, and does not usually permit of diagnosis under these circumstances. The type known as the adult form is more readily diagnosed but is usually overlooked until adolescent or adult age has been reached. Anatomically there occurs a constriction of the aorta varying from partial to complete, and usually at the site of its junction with the ductus arteriosus. Hypertension is commonly associated with this anomaly, and in all cases in which the blood pressure is

elevated without obvious cause, evidences of this lesion should be sought for. The blood pressure is elevated in the upper extremities, and diminished in the lower. There is often a perceptible lag in the femoral pulse when taken synchronously with the radial. Collateral circulation takes place principally through the intercostal, internal mammary and branches of the subclavian and carotid arteries. These vessels become



Fig. 77.—Isolated dextrocardia. Note marked cardiac enlargement, liver on right. From a case of morbus caeruleus showing at autopsy isolated dextrocardia, transposition of aorta and pulmonary artery, pulmonic stenosis, large interventricular septal defect. The electrocardiogram is similar to that shown in Fig. 76, but axis deviation is present.

enormously dilated and may be palpated as twisted cords. x-Ray reveals left ventricular hypertrophy, a prominent right border of the aorta, at times amounting to aneurysmal dilatation, and notching of the ribs caused by the dilated tortuous intercostal arteries. These cases are not infrequently encountered. I have seen 6 such, 5 in adults in which 2 were verified at autopsy, and 1 discovered on the dissecting table. In this last case there was also a stenosis of the right sub-

clavian artery. One case was that of a girl of thirteen who was referred because of an unexplained hypertension (Fig. 78).

**Valvular Lesions.**—Bicuspid semilunar valves are not infrequent, as are anomalies of other valves. They usually cannot be diagnosed as such clinically although incompetency may be present. Mitral, tricuspid, pulmonic and aortic stenosis and insufficiencies may occur. Fenestrations of valves are rather common. This defect does not permit of clinical diagnosis and

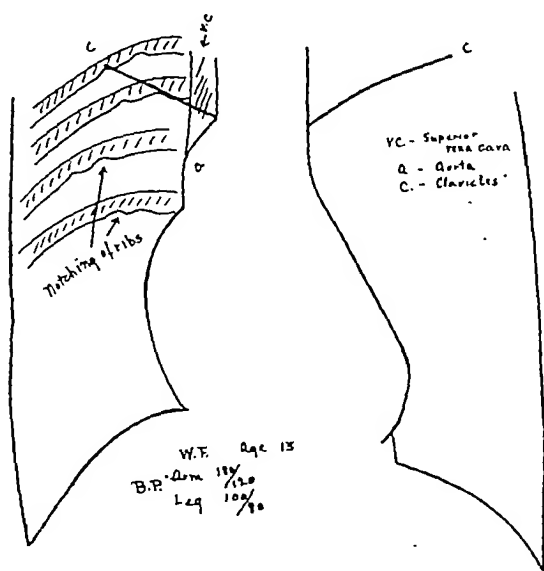


Fig. 78.—Coarctation of aorta. Orthodiagram of child thirteen years old. Note full-sized heart, absence of aortic knob and prominence of aorta to right. Notching of ribs is distinct. Collaterals were palpable in interscapular region on left.

its significance is uncertain. Lewis and Grant have pointed out the frequency with which bicuspid aortic valves become the seat of subacute bacterial endocarditis.

#### THE POTENTIALLY CYANOTIC GROUP

In these instances of arteriovenous shunt are found some of the commonly seen congenital defects such as persistent ductus arteriosus, patent foramen ovale, and defects of the interauricular or interventricular septa. It is a common mis-

take to think that the fetal passages close promptly at birth. Patten has shown that functional closure of the foramen ovale is represented by a sharply rising curve during the first six weeks of life which reaches a maximum at about three months. Complete anatomical closure may not take place in about 25 per cent of all individuals. Scammon and Norris report that obliteration of the ductus arteriosus reached its maximum at the end of three months, and that it had taken place in over

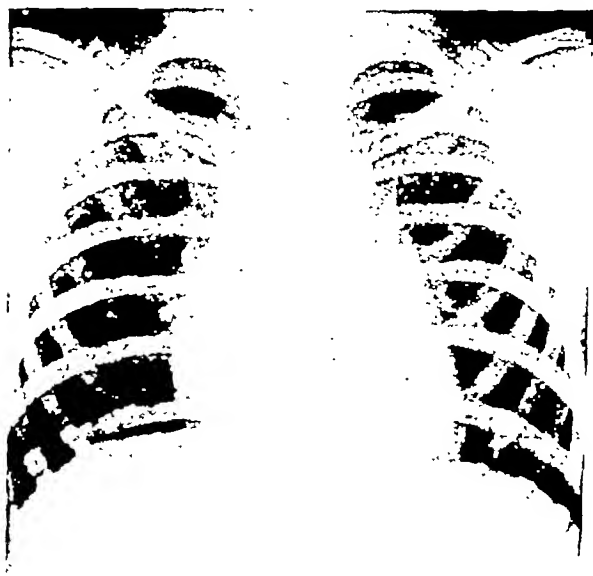


Fig. 79.—Interauricular insufficiency (septal defect). Note contour of heart and auricular enlargement. No symptoms or signs except murmur. Electrocardiogram is normal.

95 per cent of the cases examined by the end of the first year. Since the shunt in these cases is arteriovenous, cyanosis of the newborn could not be attributed to either of these lesions acting alone, and moreover the foramen and ductus are normally patent at birth. Patients in this group may usually be expected to reach adult life, and many middle age, without untoward symptoms. Cyanosis may occur transiently as a result of temporarily increased pulmonic pressure or terminally with heart failure. In any of the conditions enumerated bacterial

endocarditis, usually of the subacute type, may occur as a complicating factor.

**Interauricular Septal Defects Including Patent Foramen Ovale.**—These patients are often of delicate build, with delayed puberty. There is usually an early systolic or late diastolic murmur near the sternum in the third or fourth interspace. By x-ray examination the aorta is found to be

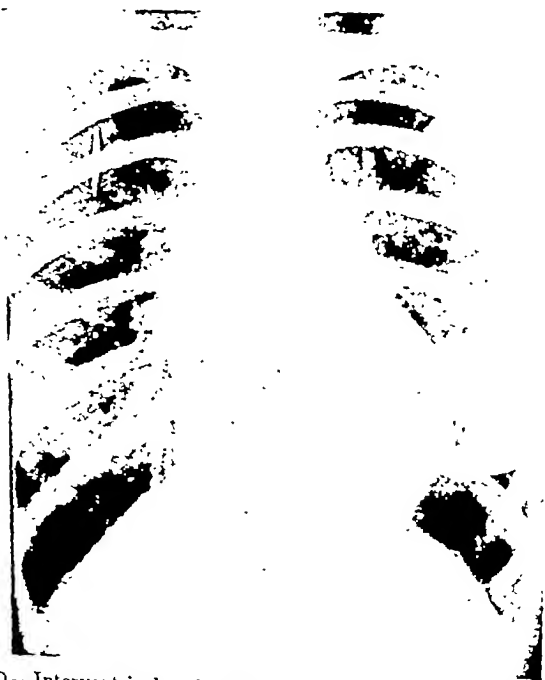


Fig. 80.—Interventricular insufficiency (septal defect). Note shape of heart and hypoplastic aorta. Electrocardiogram reveals intraventricular conduction defect. In attacks of precordial pain marked dilation of the pulmonary conus could be observed.

hypoplastic and the auricles dilated, giving a characteristic appearance to the contour of the heart (Fig. 79). The electrocardiogram shows no significant deviations from normal.

**Interventricular Septal Defects.**—*Maladie de Roger.*—The commonest site for this lesion is just below the aortic valves. I have seen 2 such cases, one in a woman of forty-eight dying of carcinoma of the ovary, with metastasis to the lungs, and one in a young girl of eighteen. The older woman

at autopsy had an interventricular opening measuring 3 mm. There had been no symptoms during life. There was present a loud harsh systolic murmur in the fourth interspace maximal about 2 cm. from the sternum. No thrill was detected, but this is not uncommonly present. The second patient has always been somewhat delicate, fatigues readily, and has occasional severe attacks of precordial pain during which the pul-

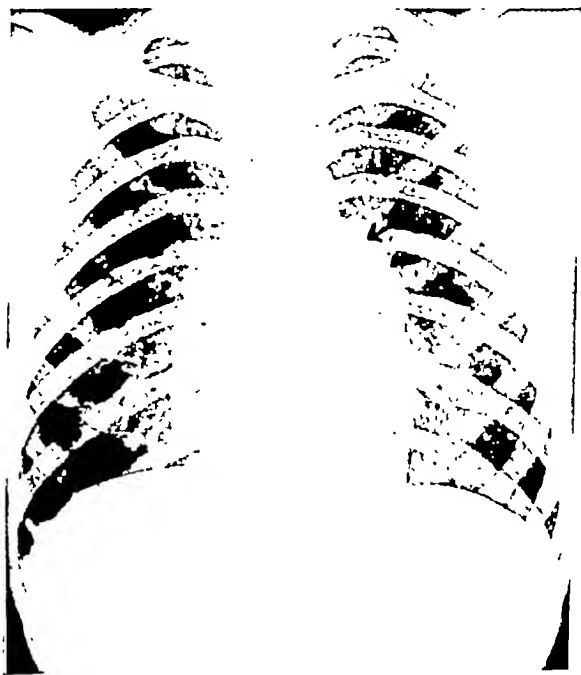


Fig. 81.—Persistent ductus arteriosus. Note prominent conus. Fluoroscopically there was marked pulsation of the conus. The typical murmur of this condition was present. There were no symptoms. The electrocardiogram is normal.

monic conus may be observed by fluoroscopic examination to be markedly dilated. Figure 80 presents the *x*-ray of this patient, showing a globular heart and hypoplastic aorta. These patients not infrequently show aberrations of the QRS waves in the electrocardiogram and this patient presented such abnormalities. The patient was normally developed. There was a loud, rough systolic murmur with a thrill in the fourth interspace near the sternum. The pulmonic sounds were re

duplicated. Cyanosis has not as yet been noted, and indeed terminal and transient cyanosis is less common in patients with interventricular septal defects than in those having defects of the auricular septum.

**Persistent Ductus Arteriosus.**—I have seen 3 cases so diagnosed, all occurring in young males. No symptoms were present in any and cyanosis had never been present. One lad ran on his school track team. In 2 of these cases the typical "machinery murmur" beginning just after the first sound, reaccentuated with the second sound and dying away in early diastole was heard maximally in the second interspace in the pulmonic valvular area. In the third case the murmur was systolic and heard in the third interspace. The pulmonic second sound was accentuated in all, due to increased pulmonic pressure resulting from the aortic-pulmonary artery shunt. Cardiac enlargement was not present in any of these cases, but it may occur. The x-ray is of great help in confirming the diagnosis, revealing a marked dilatation of the pulmonic conus, and fluoroscopically very active pulsation of this portion of the cardiac shadow may be observed. Figure 81 is the x-ray of one of the patients mentioned above. The electrocardiogram is not significant but is of help in distinguishing this lesion from pulmonic stenosis. In the latter lesion right axis deviation usually occurs.

#### THE CYANOTIC GROUP

The anomalies found in this group are often so complicated that certain diagnosis is impossible. True cases of morbus caeruleus always belong here. Such defects as total absence of the auricular, ventricular and aortic septa, or combinations of these, pulmonic stenosis and septal defects, atresia of valves with septal defects and transposition of the great vessels make up the bulk of lesions in this group. Cyanosis may be present at birth or occur subsequently. The majority of patients suffering with such lesions do not reach adult life and death often occurs a few days or months after birth. Pulmonic stenosis is the commonest defect and is usually associated with interauricular or interventricular septal defects. According to Abbott's statistics, the combination of lesions—pulmonic stenosis, defect of interventricular septum, dextroposition of

the aorta and right ventricular hypertrophy—known as the tetralogy of Fallot is the commonest of all lesions of the cyanotic group. I have seen a number of cases of congenital heart disease both clinically and at autopsy and have as yet to recognize the tetralogy. Whenever pulmonic stenosis is associated with a defect in the septum the raised pressure in the right heart leads to a venous-arterial shunt. Cyanosis becomes marked, and clubbing of the fingers is common.



Fig. 82.—Pulmonic stenosis with patent foramen ovale. Teleoroentgenogram from seven-month infant cyanotic since birth. The anterior aspect of heart is formed by the enormously dilated right auricle and hypertrophied right ventricle.

Polycythemia is often present. Dyspnea and syncopal attacks may occur.

In patients with pulmonic stenosis there is a rough systolic murmur, often accompanied by a thrill, present in the pulmonic valvular area. The pulmonic second sound is diminished. There is right heart enlargement and the pulmonic conus may become prominent. Other murmurs according to accompanying defects may be present. An infant seven months old had



been cyanotic from birth, becoming almost indigo in color during crying spells. There was cyanosis of the retina and a moderate degree of clubbing of the fingers and toes. The heart was enlarged (Fig. 82). In the third interspace there was a loud systolic murmur. There was no thrill. The pulmonic second sound was faint. Because of these signs it was reasoned that the child had a stenosis of the pulmonic valve



Fig. 83—Practical atresia of pulmonic valve. From same case as Fig. 82. The foramen ovale was widely patent.

of severe degree with a septal defect. It was thought that the systolic murmur heard was probably due to the septal defect rather than the stenosis. At autopsy there was found marked right ventricular hypertrophy, dilatation of the right auricle, stenosis almost amounting to atresia of the pulmonic valves, and a widely patent foramen ovale (Fig. 83). There is usually right axis deviation in the electrocardiograms of such patients. No tracing was obtained in the above case, but in 4 other

cases of pulmonic stenosis in which electrocardiograms were obtained such axis deviation was present in each.

In concluding the discussion of congenital heart disease, it is well to point out that except in cases with cyanosis there are no specific symptoms presented by these patients. Those with cyanosis sooner or later develop clubbing of the fingers and toes; dyspnea is commonly a symptom, and convulsions

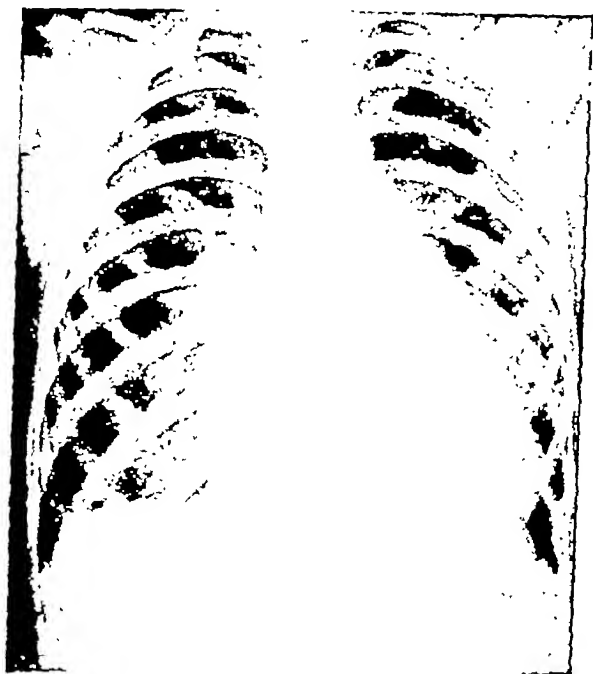


Fig. 84.—Pulmonic stenosis without septal defect or shunt—typical contour of heart. This might be confused with a mitral heart, but examination in the right oblique position revealed no left auricular enlargement. Electrocardiogram showed right axis deviation. Cyanosis was not present but may occur in this condition because of increased deoxygenation in the capillaries.

and syncopal attacks not infrequently occur; polycythemia is often present. Congestive failure with its accompanying train of symptoms may develop in any congenital lesion causing myocardial embarrassment. Precordial pain may occur and is apt to be associated with dilatation of the pulmonic artery and conus. Congenital anomalies of other parts of the body are frequently to be noted and mongolian idiocy is rather com-

monly found in association with heart disease of the congenital type.

#### RHEUMATIC HEART DISEASE: THE SIGNIFICANCE OF THE APICAL SYSTOLIC MURMUR

The typical cases of rheumatic fever with joint symptoms or chorea need no discussion in this paper. However, in infancy and early childhood such typical cases are rarely seen. The rheumatic infections, including chorea and tonsillitis, are the most important causative agents in the production of heart disease in young people. It is therefore of importance to recognize atypical forms of this disease. In my experience, well over 25 per cent of adults with mitral stenosis give no history identifiable with that of rheumatic fever or chorea. The occurrence of vague aches or pains either in the muscles or joints of children should lead to a strong suspicion of rheumatic disease unless other explanation be afforded. In children who suffer from repeated attacks of tonsillitis the heart should be watched constantly. I recently saw a child of four stated to be normal by competent observers up to the age of three, but who had had frequent bouts of tonsillitis and who in the midst of such an attack became edematous. There was low-grade fever, dyspnea, generalized edema, and pleural effusion. An obvious mitral stenosis was present at this time. The child died twenty-four hours later. This child for the past year had suffered from nutritional disturbances, and nausea and vomiting had occurred often. Vomiting is frequently a symptom to be found in the rheumatic child, and may occur during periods of apparent good health. Doubtless this child had suffered from continuous low-grade rheumatic infection or at least frequent recurrences of such infection for some time.

Whenever a clearly defined valvular lesion is present in a child, it may be assumed that damage to the heart has occurred some time before its discovery, for such lesions do not manifest themselves during the course of an ordinary acute rheumatic infection. They become obvious when an infection has lasted some time, or has been recurrent.

Epistaxis is common in these children, and, while not diagnostic of itself, when occurring with other suggestive evidence,

points toward rheumatic infection. Abdominal pain may occur and if associated with nausea and vomiting may lead to the diagnosis of surgical abdomen. The occurrence of rheumatic nodules along the course of tendons and ligaments, and in the scalp is all too often overlooked, and when present they are invaluable in arriving at a correct diagnosis. They may persist long after active infection has apparently subsided. Skin rashes are at times present and may take the form of erythema multiforme.

Frequently the disease manifests itself only as an obscure malaise, with lassitude and unusual fatigability. There may be little or no fever. When the heart is involved there is almost always a tachycardia out of proportion to the severity of the illness or the height of the fever. Occasionally, however, I have seen bradycardias of sinus origin. Systolic murmurs are wont to occur over the precordium. I place less stress on these than on any other sign. It is true that they may be due either to actual valvulitis or to relaxation of a ring. However, they are so commonly present in febrile disease of any sort, in tachycardias, and in states of malnutrition that their presence cannot be emphasized as indicating actual cardiac damage. But when such a murmur appears during a suspected attack and lasts after the illness is apparently over, it is of more significance. If definite mitral stenosis or aortic lesions appear in long lasting illness, the diagnosis is certain. Dilatation of the heart out of proportion to the illness is strongly suggestive of cardiac involvement.

The occurrence of evidences of inflammation of the pleura and pericardium is of great importance. Pericarditis with a large effusion is not difficult to recognize. However, a friction rub may be the only evidence present, and the amount of fluid may be too small to recognize clinically. Pain over the precordium is not uncommon in pericarditis and indeed may occur in rheumatic carditis when pericardial involvement is not present. I recall a youth of fourteen who had had vague aches in his left shoulder, and had felt tired and run down for several weeks, who suddenly complained of precordial discomfort and breathlessness, and who on examination had a typical pericardial friction rub. He had a pulse of 120, and a temperature of 100° F. The heart sounds were clear. x-Ray

examination of the heart was negative. There was a moderate leukocytosis and the sedimentation rate was rapid. He was in bed four months with weakness, fatigability, tachycardia, and at one time a clear, straw-colored effusion into the right pleura. There was slight fever from time to time. When re-examined one year after recovery there was a definite mitral stenosis. Pleural effusion not infrequently occurs during the course of rheumatic infections.

Edema may at times be present. It has been my experience, as well as that of others, that edema occurring in rheumatic heart disease in children coming to autopsy is inevitably associated with an active infection of the heart, whether very definite clinical signs of activity have been present or not. Most frequently such edema is undoubtedly associated with heart failure. However, I have seen several cases in which it partook of the nature of nephrotic edema, being diffuse in character, and associated with considerable amounts of albumin in the urine, and a diminution of the serum protein. The case of a child of three coming to autopsy also had cholesterolemia. There was mitral stenosis, and an active valvular endocarditis of the rheumatic type. It should also be remembered that a constrictive pericarditis may lead to engorgement of the viscera and ascites. I have seen one such case in a child.

Laboratory findings are at times of considerable aid in the diagnosis of rheumatic heart disease. This type of infection is one of those most commonly associated with a rapid sedimentation rate of the erythrocytes and the sedimentation test should be done on all suspected cases. This test is unfortunately not diagnostic since an augmented rate occurs in many other conditions. However, when rapid in suspected cases, it gives further weight to the diagnosis. I have found it to be of more value in determining activity of infection in known rheumatic individuals. The rapid rate may persist long after other signs of infection have subsided. There is generally some degree of leukocytosis, and in protracted or severe cases definite anemia may occur.

In my experience the electrocardiogram gives invaluable aid in about one third of the cases. During periods of activity prolongation of the auriculoventricular conduction time is the most common abnormality noted. Abnormalities of the ST

segments and T waves also occur. Figure 85 is the electrocardiogram obtained from a colored child subject to recurring episodes of listlessness and slight fever, during such an illness. Four years previously there had been a typical attack of rheumatic fever, at the onset of which, however, the child already had mitral stenosis. Following that attack an aortic insufficiency developed. This electrocardiogram illustrates both prolongation of the auriculoventricular conduction time and aberrations in the ST segments. Changes in the ST segments

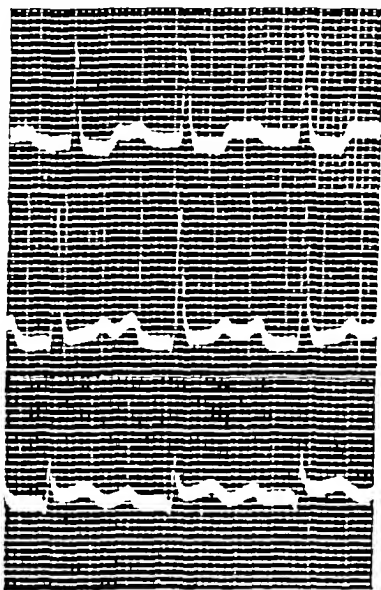


Fig. 85.—Active rheumatic carditis. Prolongation of auriculoventricular conduction time (PR interval 0.28 second). Note high take-off of ST segments in Lead 3.

and in the T waves may at times only be present in the precordial lead; therefore this lead should be routinely taken in suspected cases.

The x-ray offers little help in early cases. In those in whom large pericardial effusions have occurred, there is noted enlargement of the heart of a rather typical contour. If definite valvular lesions are present, the x-ray usually reveals changes in the contour of the heart and in its size, according to the lesions present.

**The Apical Systolic Murmur.**—The typical valvular lesions of rheumatic heart disease, mitral stenosis with or without aortic insufficiency and stenosis, offer little difficulty of diagnosis and will not be discussed further. Evaluation of the significance of systolic murmurs heard at the apex, transmitted or not transmitted, offers one of the most troublesome problems of cardiac diagnosis. It must be remembered that such murmurs are not uncommonly transient, and may occur in normal children as a result of exercise, excitement, or tachycardia due to any cause. They may be present in anemia, malnutrition or fever. They may occur rather obviously only during some phase of respiration; or when the patient is only in one position. Under these circumstances, and when associated with no other evidence of heart disease, I am inclined to attach no cardiac diagnostic significance to them. When they are persistently present, especially in a child who has had rheumatic fever, or in whom there is good reason to suspect rheumatic infection, I think they cannot be lightly dismissed. We have already seen that the murmurs of certain congenital lesions may be heard near this area. In many cases of mitral stenosis the diastolic or presystolic murmur is heard with difficulty or not at all, an apical systolic murmur alone being present. The diastolic murmur may be heard only in a very limited area, and the region of the apex should be gone over carefully, and the ear trained to detect this low-pitched sound. Exercise may bring out this murmur, and I have found that I can more frequently hear it with the patient lying on the left side. When demonstrated, there is little doubt of the diagnosis of structural valvular disease. If it cannot be demonstrated, then a systolic murmur with reversal of the character of the first and second sounds at the apex, dup-lub rather than lub-dup (the second sound may be considerably diminished or absent), together with an accentuation of the pulmonic second sound indicates mitral stenosis. Enlargement of the heart to percussion or by x-ray examination indicates heart disease, but not necessarily valvular disease. In mitral lesions on percussion there is apt to be an extension of the heart border to the upper left, with or without recognizable cardiac enlargement, due to prominence of the pulmonic conus and dilatation of the left auricular appendage. Roentgeno-

graphic examination shows a prominence of the second and third curves of the left border of the heart (pulmonic conus and left auricular appendage) and when the heart is viewed in the right oblique position, dilatation of the left auricle, which lies entirely posterior to the heart in the anteroposterior view except for the appendage, may be seen. These findings may be present in the absence of any recognizable increase in the diameters of the heart as usually determined in the anteroposterior view. Should all other evidences of heart disease mentioned above be absent, in my opinion a systolic apical murmur in a child suspected of rheumatic disease should still be viewed with suspicion for some time to come; often other signs develop later or the murmur may disappear. This, however, does not imply that any restrictions should be placed upon such a child if it be otherwise in good health. It should be remembered that a pure mitral insufficiency is an exceedingly rare valvular lesion. I have never seen an instance proved at autopsy; however, it has been reported.

#### BACTERIAL ENDOCARDITIS

It is not my purpose to discuss this subject at any great length. Adequate descriptions may be found in any textbook on medicine or heart disease. I do wish to stress that the subacute form of bacterial endocarditis may have a very insidious onset. A girl of eight was brought into the hospital following a left hemiplegia occurring suddenly the evening before. She had attended school that day. There was no definite history of illness of any kind preceding the hemiplegia, but the child had been tired, unusually quiet, and had avoided play for some days. An obvious mitral stenosis was detected, and *Streptococcus viridans* was cultured from the blood. This child lived for a year and during that time had an embolic occlusion of her anterior tibial artery and emboli elsewhere. When blood cultures are negative, rapidly developing valvular lesions, a septic type of temperature curve, enlargement of the spleen, clubbing of the fingers, petechiae and the occurrence of embolic phenomena are of the greatest importance in arriving at a correct diagnosis. The retinal and conjunctival arteries should always be examined for hemorrhages of embolic and petechial origin and the occurrence of exquisitely



sensitive points in the fingers and toes with or without tumefaction are significant of small emboli. Recurrent attacks of pain in the left upper quadrant of the abdomen frequently accompany infarction of the spleen. Patients with congenital or rheumatic heart disease are particularly prone to develop such infective endocarditis.

#### PERICARDITIS

Large accumulations of fluid in the pericardial sac are not difficult to recognize from the physical signs and x-ray. Such effusions may be almost symptomless, and the presence of symptoms depends upon the amount of interference with the diastolic filling of the heart. On the other hand, small effusions which accumulate rapidly and before the pericardium has stretched may produce striking symptoms such as dyspnea, paradoxical pulse and cyanosis, and it is not uncommon to see such symptoms disappear, even though the physical signs indicate an increasing amount of fluid, perhaps to reappear again when the pericardium is greatly distended. Daily record of the measurements of the heart should be kept, and a steady increase in the size is of the greatest importance in the diagnosis. Friction rubs are usually present at some time and may persist throughout. The heart sounds become more difficult to hear, and it is very helpful if the apex beat can be palpated far inside the border of percussion dulness. The percussion dulness at the base of the heart is broadened and may diminish in extent on changing the patient from the prone to the upright position. Physical signs of atelectasis of the lung may occur on the left at the angle of the scapula. The x-ray reveals a general enlargement of the heart shadow with an obliteration of the usual demarcations between its chambers.

Effusions of less than several hundreds of cubic centimeters cannot be recognized by physical signs or x-ray. This is of no great importance except in those cases in which the effusion is purulent. It is of the greatest importance to recognize such cases of pericardial abscess early, for in general the sooner drainage is instituted the better chance the patient has to recover. In any illness in which a purulent pericarditis may occur, such as pneumonia, empyema, etc., pericardial friction rubs should be watched for as the earliest and often the only definite indication of pericardial involvement. In these cases

the temperature begins to run a septic course. The electrocardiogram may present suggestive evidence and when this is the case it is generally noted that the ST segments take off high, usually in all leads (Fig. 86). In the nonpurulent forms pericardial tapping is rather infrequently necessary to relieve symptoms, except in those of tuberculous origin. When purulent pericarditis is suspected, tapping may be resorted to for diagnosis. Because of adhesions or pocketing of the effusion, a dry tap may result. If within several days it has not been

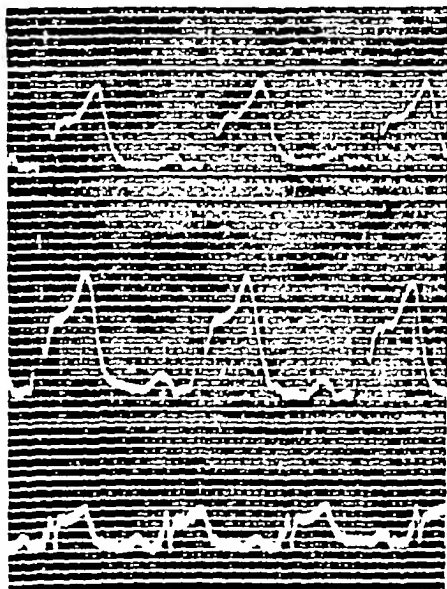


Fig. 86 —Purulent pericarditis complicating pneumonia. Note very high take-off of ST segments in all leads.

possible to make the diagnosis certain, and if there is strong evidence of pericardial abscess, or if the diagnosis of purulent pericarditis is reasonably certain without tapping, the pericardium should be opened surgically and drainage established.

As a result of any inflammation of the pericardium adhesions between the visceral and parietal layers are prone to occur. These do little harm unless tight bands constrict the auricles or orifices of the great veins, or the scar tissue contracts so that diastolic filling of the heart is impeded, or in addition to the obliteration of the pericardial cavity, the peri-

cardium is adherent to the mediastinum, pleura and diaphragm. Under this last circumstance great hypertrophy of the heart and eventual failure result. The first two types are of great interest since they lead to increased venous pressure, and stasis in the liver resulting in cardiac cirrhosis and ascites. Suggestive signs of chronic pericarditis are systolic retraction of the interspaces, failure of the axis of the electrocardiogram to change with change in the position of the patient, and on x-ray examination irregularities in the contour of the heart. failure of the heart to descend with inspiration, and but slight difference in the systolic and diastolic size of the heart may be noted. In the constrictive type of chronic pericarditis there is often no cardiac enlargement.



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### THE DIAGNOSIS AND TREATMENT OF OTITIC MENINGITIS

THE most common cause of meningitis, excluding the meningococcic and tuberculous forms, is otitic infections. Otitis media is, therefore, a serious infection, primarily because of its complications. Prevention is the best treatment, and careful, understanding observation of every middle ear infection will lead to earlier recognition of the serious sequelae.

The onset of an intracranial complication following a middle ear infection may develop almost immediately after the appearance of the otitis, or it may run a subacute course with relatively few symptoms other than draining ear, and a complication will become manifest at the time the patient is thought to be out of danger. In infants, the ear infection may easily be overlooked until after meningeal invasion has occurred. The course which a middle ear infection may take depends upon the organism, its virulence, and the route of infection which it follows in the temporal bone. The infection may involve the labyrinth, the pneumatized mastoid cells, or the petrous pyramid. From these foci the infection may extend along thrombosed and infected vessels in the bone into the subarachnoid space and brain, and by direct invasion of the leptomeninges from the labyrinth. If the mastoid cells or petrous pyramid become infected, there may be a gradual necrosis of bone and dura, with extension of the infection into the subarachnoid space, brain, or lateral sinus. Therefore, the intracranial infection may be rapid when it travels by way of the labyrinth or infected vessels, and more deliberate when extension occurs through bone and dura. When the mode of ex-

tension is retrograde through the vessels, there may be a rapid intracranial complication without any warning signal. Infections in the labyrinth produce signs of labyrinthine irritation such as vertigo, vomiting, and nystagmus. When the infection takes a more deliberate route directly through bone, the patient usually shows evidence of definite mastoid infection, with pain and swelling of the ear and skin over the mastoid process and persistent discharge from the ear. However, this external evidence may be lacking in some mastoid infections and usually when the petrous pyramid is infected. Once an infection is thought to be present in the temporal bone, procrastination concerning operation may be the cause of an intracranial complication.

The intracranial complications which may follow middle ear infection are meningitis, brain abscess, infective sinus thrombosis, epidural abscess, involvement of cranial nerves by local meningeal reaction, such as described by Gradenigo,<sup>1</sup> and nonsuppurative encephalitis. Occasionally the facial nerve may be paralyzed by necrosis of bone in the region of the facial canal.

#### DIAGNOSIS

Any inflammatory reaction of the meninges may be termed a meningitis, but the fundamental differential is whether the meningeal reaction is sterile or whether it is due to the actual presence of bacteria in the subarachnoid space. A patient may have all the clinical signs of meningitis with a pessimistic outlook only to find that the patient makes an uneventful recovery.

The appearance of symptoms indicating meningeal invasion in a patient with an ear infection should be recognized as early as possible. Headache and mild rigidity of the neck, together with some degree of febrile rise are the earliest symptoms. It is during this period that eradication of the focus may be possible by operative procedure on the mastoid bone. If a mastoid operation has already been done the symptoms may indicate that a walled-off focus was not exposed in the original operation. The impression that the patient is doomed because of these early symptoms is entirely unwarranted, because it is often at this stage that the patient has a cellular reaction

in the meninges without actual invasion by bacteria. As the infection spreads through bone to the epidural surface, there is a reactive process in the dura which attempts to wall off the infection with the formation of an epidural collection of pus. If this is not drained, the inner wall of the dura becomes involved in the extension and again inflammatory reaction is thrown out in advance of bacterial invasion, producing a sterile localized reaction of the leptomeninges. If the spinal fluid is examined at this stage, the cerebrospinal fluid pressure may be slightly increased and microscopic examination will show the presence of a few up to several thousand cells per cubic millimeter. The fluid should be cultured immediately and after culture the fluid centrifuged and smears made to determine the presence of bacteria. In this early stage of sterile meningeal reaction, no time should be lost in attempting to find and eliminate the focus of infection. If operation has previously been done, a second exploration should be considered in the hope of finding a walled-off focus which was not removed at the first operation.

Within twenty-four to forty-eight hours after the initial symptoms of headache and mild rigidity of the neck, the temperature begins to rise rapidly to a level around 104° F. to 105° F., the pulse becomes rapid, the cervical rigidity becomes increased, headache is severe, the patient becomes very restless with later development of delirium, there is a generalized hyperesthesia over the entire body, the Kernig sign is positive, and there may be cranial nerve palsies secondary to the meningeal reaction. At this stage, examination of the spinal fluid gives every indication of the actual presence of organisms in the subarachnoid space. The cell count ranges, as a rule, from 1000 to 5000, and in some instances may reach 35,000 to 40,000. The globulin is increased, the total protein ranges from 75 to 150 mg. per cent, and there is marked reduction or absence of spinal fluid sugar, and decrease in spinal fluid chlorides. The spinal fluid pressure usually ranges from 200 to 400 mm. of water. The cytology of the spinal fluid shows a predominance of polymorphonuclear leukocytes and smears show the presence of organisms.

In a report by Neal, Jackson, and Applebaum<sup>2</sup> on 231 cases of meningitis following otitis media and sinusitis, 121 were

due to streptococci, 75 to pneumococci, 20 to the influenza bacillus, and the remaining 15 to staphylococci, streptothrix, *Bacillus coli*, *B. friedländeri*, and torula.

### TREATMENT

The treatment and prognosis depend upon whether the meningitis is sterile or infective, and on the organism. Cultures should be taken from the ear at the time of paracentesis and from every mastoid operation so that if meningitis subsequently develops, the organism causing the ear infection will be known in case the spinal fluid is sterile. In all cases of sterile meningitis, the mastoid should be operated upon immediately, so that drainage may be instituted at the source of the infection. Spinal drainage should be done once or twice daily until clinical improvement occurs and the spinal fluid approaches normal. Hypotonic glucose, 0.45 per cent, from 500 to 1000 cc., given an hour before drainage will increase the flow of cerebrospinal fluid. By early recognition of the preinfective or sterile stage of meningitis, infective meningitis can often be prevented.

Recoveries from infective otitis meningitis have been reported from time to time, but this is accepted as a rarity. Dwyer<sup>3</sup> states that he has seen 367 cases of meningitis, with 18 recoveries. In a series of 623 cases of meningitis, excluding meningococcic and tuberculous types, Neal, Jackson, and Applebaum<sup>2</sup> state that 16 patients recovered. Of these, 121 cases were streptococcic infections due to otitis media, mastoiditis, and sinusitis, with 9 recoveries.

The recent use of para-amino-benzene-sulfonamide in the treatment of streptococcic infections<sup>4, 5, 6, 7</sup> is most encouraging. Approximately 50 per cent of all otitic meningitis is due to hemolytic streptococci, and if treatment is instituted early, recovery may be expected in this type in the majority of cases. Too few cases have been treated with the drug to arrive at definite conclusions, but in a series of 6 cases of hemolytic streptococcic meningitis and 2 cases of sterile meningitis secondary to streptococcic mastoiditis,<sup>8</sup> all recovered except 1. The following case illustrates the course and treatment of an otitic hemolytic streptococcic meningitis with recovery.



S. B., white male, age seven, was admitted to the South Baltimore General Hospital on March 2, 1937. On February 25, 1937, the child had earache on the left side, with purulent discharge from the ear on the following day. Later in the afternoon the drainage from the ear ceased and a paracentesis was done. The child was sluggish, complained of headache, and was feverish. On March 2 he was very drowsy and was found to have marked cervical rigidity. The examination on admission showed mild delirium and marked rigidity of the neck. The skin was flushed and hot. A purulent discharge was present in the left external auditory meatus. There was some swelling over the mastoid tip with tenderness. The deep reflexes were present and active. The Kernig sign was positive.

The patient was seen by Dr. Nathan Snyder and the diagnosis of mastoiditis with meningeal irritation was made. A left simple mastoidectomy was done and the mastoid cells were found to be necrotic and filled with a thin purulent exudate. The following morning a spinal fluid examination was done by Dr. Louis McIlhenny, and the fluid was found to be cloudy, contained 13,760 cells, was under a pressure of 380 mm. of water, smear showed gram-positive cocci, and after culture a hemolytic streptococcus was identified. The patient was seen by Dr. Richard G. Coblentz and treatment was begun with sulfanilamide (para-amino-benzene-sulfonamide). The temperature course is shown in Fig. 87 and the treatment and laboratory findings are shown in Fig. 88. The patient showed an immediate improvement in the spinal fluid findings, but his clinical course was very stormy. On the fourth day after treatment was begun he was definitely improved, showed less rigidity of the neck, and was more alert. On March 13 his temperature rose to 105° F., the mastoid incision was widened for better drainage, the patient appeared very toxic, and his neck was still quite rigid. On March 13 and 16 small transfusions were given. From this point on there was slow but gradual improvement with a gradual decline of the temperature by lysis, and after April 1 the temperature did not exceed 100° F. rectally. The drainage from the mastoid incision and ear gradually decreased and when he left the hospital on April 18 the wound was healed and the discharge from the ear had ceased entirely. Three weeks following discharge from the hospital, he was again examined and was found to be in excellent health, was gaining weight, and had no complaints.

From Fig. 88 it will be seen that in the treatment the drug was administered by the oral, subcutaneous, and intrathecal routes. At the beginning of treatment in meningitis, the oral administration cannot, as a rule, be relied upon because of the uncooperative state of the patient. The calculated daily dose should be given in two infusions of 1 per cent solution in normal saline, eight to twelve hours apart. In preparing the solution, the salt solution should be brought to the boiling point and after cooling a few degrees, the powdered sulfanilamide added slowly. No further sterilization is necessary. The

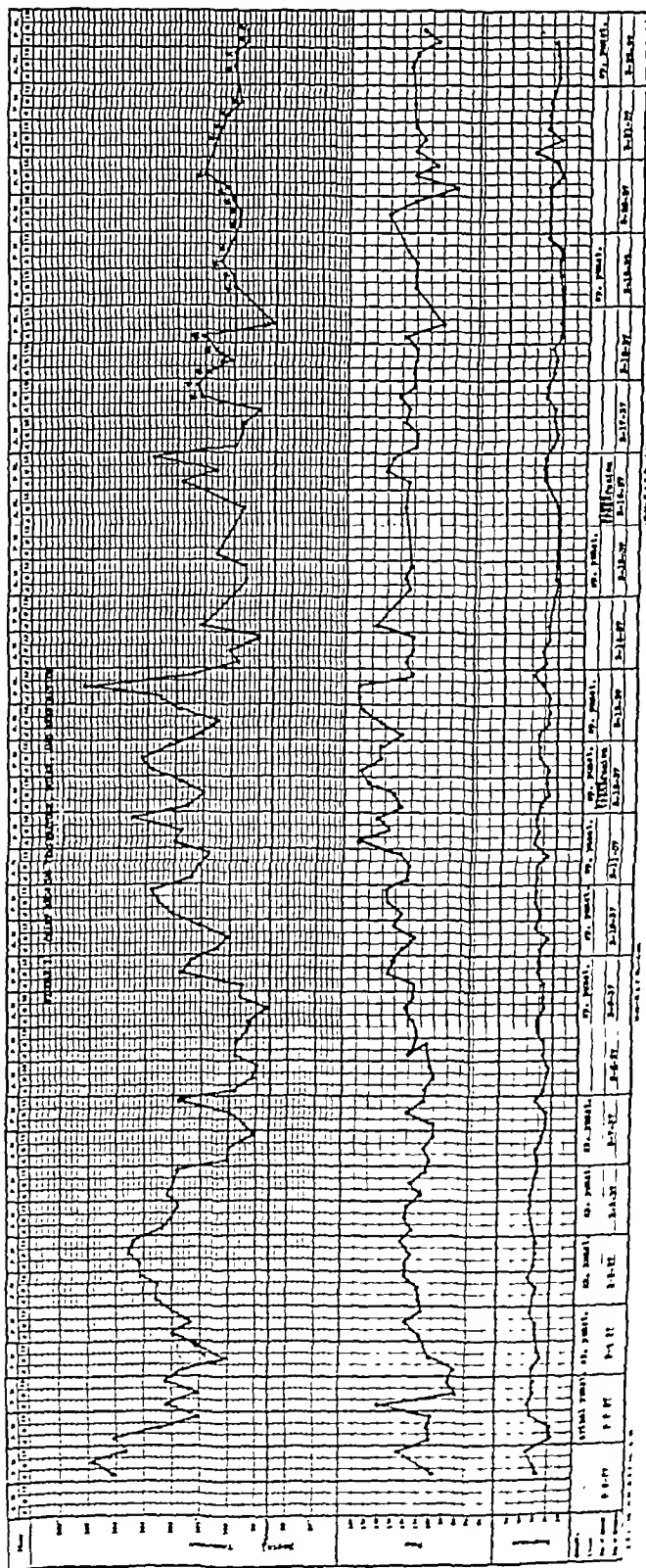


Fig S7.—Chart showing temperature, pulse and respiration. (Continued on p. 1319.)



Concerning the intrathecal administration, the exact requirements have not yet been determined. In 7 of the 8 cases of streptococcic meningitis treated by me, the drug was given intrathecally once a day in a dose ranging from 25 to 50 cc. of a 1 per cent solution. This was continued until at least 3 negative spinal fluid cultures were obtained. In the case just described, 5 injections were given after the spinal fluid became negative, because of the stormy course. However, in 1 case of the series, only 1 intrathecal injection was given and the patient made a prompt recovery.

In computing the dose, an average of 1 Gm. per 20 pounds of body weight every twenty-four hours has been advocated by Long.<sup>6</sup> Children will tolerate much larger doses, but whether this is necessary has not yet been determined. In two children weighing 50 pounds, 6 Gm. a day were well tolerated.

The majority of patients receiving the drug will develop varying degrees of cyanosis, but this clears up rapidly after administration is stopped. A moderate anemia may develop after prolonged use, and in patients who have an idiosyncrasy to the drug, an occasional severe hemolytic anemia may occur, as shown by the excretion of urine of port-wine color. If acidosis occurs, alkalis should be administered. Therefore, during the treatment the hemoglobin, red count, carbon dioxide combining power, and urine should be carefully watched.

As previously stated, the treatment of otitic meningitis depends upon whether it is sterile or infective and the causative organism. The preliminary work on streptococcic meningitis indicates that a fair percentage of recoveries can be expected when treated by sulfanilamide, so that if the original otitis media or mastoiditis is known to be due to hemolytic streptococci, this drug should be employed. If the causative organism in the original infection is not known and the spinal fluid shows the absence of organisms, it would seem worth while to use sulfanilamide because of the high percentage of streptococcic infections in otitic meningitis. In dealing with streptococcic meningitis where sulfanilamide therapy is used, the advisability of doing a mastoidectomy is an open one. The first case I treated had a severe mastoid infection, but the operation was deferred until after the spinal fluid cultures were negative. In another case, the mastoid was not operated upon

and the prompt cessation of discharge from the ear and the recovery of the patient suggest that mastoidectomy may be unnecessary in hemolytic streptococcic infections.

CHART SHOWING LABORATORY FINDINGS AND RECORD OF TREATMENT								
DATE (1937)	CEREBROSPINAL FLUID			BLOOD		TREATMENT (sulfadiazine)		
	Cell Count	Pressure (mm. H <sub>2</sub> O)	Culture	WBC	REC (millions)	Oral (gm.)	Subcut. (cc. 1% solution)	Intrasp.
March								
3	13760	380	+ hemolytic streptococci	34,000	4.1	-	150	50
	6740							
4	1760	250	+	-	-	-	350	47
5	1000	356	smear + cult. -	24,800	3.3	-	350	40
6	780	300	neg.	27,200	3.2	-	415	35
7	408	294	smear + cult. -	-	-	-	-	40
8	149	250	neg.	42,000	3.9	3	-	50
9	1740	240	"	20,200	-	4	-	42
10	478	228	"	30,200	3.8	4	-	40
11	340	248	"	19,200	-	6	-	45
12	410	220	"	21,600	3.1	6	-	40
13	660	280	"	17,200	-	6	-	40
14	410	230	"	-	-	6	-	-
15	285	270	"	14,800	3.8	6	-	-
16	126	222	"	10,400	-	5	-	-
17	106	250	"	10,800	-	5	-	-
18	79	160	"	9,800	-	5	-	-
19	77	152	"	10,000	-	5	-	-
20	-	-	-	12,800	4.5	5	-	-
22	11	170	neg.	11,200	-	5	-	-
24	-	-	-	10,600	-	2	-	-
25	-	-	-	9,800	-	2	-	-
30	-	-	-	8,400	-	2	-	-
31	-	-	-	-	-	(discontinued)	-	-
April 7	-	-	-	12,600	4.7	-	-	-
8	29	162	neg.	-	-	-	-	-

Fig. 88.

If the original otitic infection is due to an organism other than hemolytic streptococci and the meningitis is still in the sterile stage, mastoidectomy should be done as early as possible. By so doing, the entrance of organisms into the subarachnoid space may be prevented.

If the meningitis is of pneumococcic etiology, sulfanilamide may be tried, but my experience in 2 cases is discouraging. Both of these patients showed a clinical course modified from the usual untreated pneumococcic meningitis, but death occurred in both cases. Patients with pneumococcic meningitis may recover occasionally with specific antipneumococcic serum and it may be worth while to combine serum and sulfanilamide. However, no satisfactory treatment for pneumococcic meningitis has yet been devised.

Approximately 20 per cent of all otitic meningitis is due to organisms other than streptococci and pneumococci. Since there is no specific treatment, daily spinal drainage and general supportive treatment should be employed.

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## CLINIC OF DR. EDWARD A. LOOPER

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### INFECTION OF THE NASAL ACCESSORY SINUSES IN CHILDREN

FREQUENT colds associated with nasal discharge generally mean infection of some of the accessory sinuses. It is now generally recognized that a so-called "common cold" which does not clear up in two weeks' time has become complicated by invasion into some of the sinuses and if left untreated will result in serious disease. This is particularly true in infants and young children, for we know that the constantly "running" nose in a child demands definite attention if the child's future health and development be given the serious consideration it deserves. Children with infected sinuses are irritable, anemic, undernourished and present all the symptoms associated with an active focus of infection. Furthermore, such infections retard the development of the sinuses themselves so that a condition is left for the continuance of a chronic disease which might have been prevented if early treatment had been instituted.

It is a common practice to attribute all chronic colds and all cases with nasal discharge, regardless of location, character or amount of secretion, to diseases of the tonsils and adenoids. It is often taken for granted that this is the only factor to be considered, while in fact the true source of the infection may be in the paranasal sinuses. The importance of investigating this field is impressed upon us when we frequently encounter children who have had their tonsils and adenoids removed, but who do not get the desired relief of their symptoms. They give a history of colds being as frequent and the nasal discharge as constant and as severe as before operation. The operation is frequently considered as an unjustifiable pro-

cedure, the results being unsatisfactory to the patient and embarrassing to the surgeon. A situation of this kind can be avoided if more attention is paid to the sinuses before the tonsils and adenoids are removed. In all cases of children with inflammatory lesions around the nose and throat, where the nasal symptoms predominate, the sinuses should be examined. Where there is a great deal of sneezing, congestion of the turbinates, constant colds with thick profuse nasal discharge, a careful investigation of the sinuses is called for.



Fig. 89.—Orbital abscess from an infected antrum. In an infant three weeks of age.

If the diagnosis is correctly made, treatment can be properly instituted and the results will be satisfactory.

While children are not as susceptible to diseases of the sinuses as adults, the condition is frequent enough to require careful consideration. In fact, the subject requires more attention than is generally given to it by rhinologists. Haike<sup>1</sup> made an autopsy study of 394 cases of children. He opened the sinuses of 62 cases and found 52 of this number diseased. The ages were from nine months to thirteen years. Forty-



seven cases had an infection of the maxillary antrum, 2 of the sphenoids and 3 had an involvement of the ethmoid cells. Dean and Armstrong<sup>2</sup> investigated the sinuses in a group of children presenting the common symptoms of infected tonsils and adenoids. One hundred and forty-five cases were examined, and of this number 65 showed some definite involvement of the sinuses. In a similar group of cases White<sup>3</sup> made x-ray studies of 50 children who had been admitted to the hospital for tonsillectomy and adenoidectomy and out of the 50 cases 41 showed pathologic sinuses.

Apparently one reason why this condition is not suspected more frequently is that there is still a prevalent opinion that the sinuses in children are so undeveloped that they do not play an important part in the etiology of early nasal in-



Fig. 90.—Severe orbital abscess in a child six weeks old.

fections. In an effort to clarify this misconception, I will briefly mention our present knowledge of the anatomic construction of the sinuses in infants and children. Considerable work along this line has been accomplished by Onodi<sup>4</sup> who has made an extensive anatomic study of 102 skulls. The material was obtained from fetuses six and a half to eight months, from the newborn, and from children one to nineteen years of age. Since his work, our knowledge of this subject has been further supplemented by the valuable investigations of Davis<sup>5</sup> and more recently by the contributions of Schaeffer.<sup>6</sup> The general opinion is that the frontal sinus makes its appearance from the end of the first year to the beginning of the third year.<sup>7</sup> It develops slowly and is about the size of a pea between the sixth and seventh years. From the seventh to the

ninth year it is recognized as a distinct cavity. The maximum development is reached during the nineteenth year, when it measures from 16 to 21 mm. in height and from 21 to 24 mm. in width.<sup>8</sup> The sphenoid sinus is merely a faint depression in the body of the sphenoid bone at birth. Its real development begins at the end of the fourth month and generally increases in size until the sixteenth year. The ethmoid cells are present in the newborn, as shown by Curran<sup>9</sup> who dissected fetuses from three and one-half months to birth. They develop in size with advancing years until puberty. The

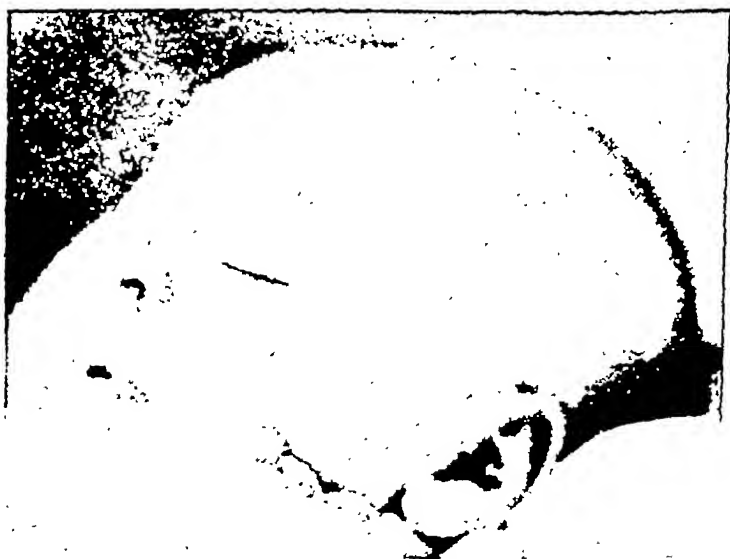


Fig. 91 —Infected ethmoids. Child one month old.

maxillary antrum is most frequently infected in the child, as it has the earliest and greatest development. According to Gegenbaur,<sup>10</sup> "The first rudiment of the maxillary antrum is the first to appear, being seen even before the middle of fetal life, but it does not attain its complete development until comparatively late, nor does it show any considerable growth before the second year of childhood." At birth it occupies a small space to the inner side of the orbit.<sup>11</sup> The subsequent development is downward, assuming its full shape after the eruption of the permanent teeth. The maximum development

is attained between the fifteenth and eighteenth years. So we find the maxillary antra and ethmoid cells present at birth, while the frontals and sphenoids make their appearance before the third year. Therefore from an anatomic standpoint the sinuses in early life are sufficiently developed to be taken into consideration in pathologic processes. It is true that the sinuses in children are not always perfectly developed, for even in the adult we know of no structure in the human body which is subject to such wide variations in size, structure, location and development as the accessory sinuses.

In the early years of childhood the upper respiratory tract is particularly susceptible to infection and is generally involved in most of the exanthematous diseases. In practically



Fig. 92.—Infected ethmoids. Orbital abscess, age three years.

every case of measles, whooping cough, diphtheria and scarlet fever, severe reactions are produced in this area. We are always on the alert for ear involvement following these diseases, but do we pay sufficient attention to nasal complications?

The sinuses are lined with mucous membrane similar in structure to that of the eustachian tube, and by the process of continuity can be readily infected. The numerous recesses and cavities adjoining the nasal fossae produce an ideal location for the implantation and development of organisms. If bacteria are placed upon the smooth unobstructed mucous membrane of the mouth we know that they will be eliminated by the normal douching action of the oral secretions as demonstrated by Bloomfield's<sup>12</sup> work. However, when they lodge

in obstructed crevices like the tonsillar crypts, reduplicated nasal mucous membrane or sinus cavities, they remain for a



Fig. 93.—Orbital abscess. Ethmoid infection. Age nine years.



Fig. 94.—Orbital abscess. Frontal and ethmoid infection

much longer time. If the body resistance is below normal, or if the predominating organisms are of a very virulent strain, the defensive action of the tissues may not be able to resist

infection. When the sinuses become extensively infected, eradication of the disease is extremely difficult. Congested nasal mucosa, hypertrophied turbinates, septal deviations, small nasal cavities, all interfere with ventilation and drainage, thus prolonging a condition which could be easily eradicated in a more accessible environment.

### DIAGNOSIS

The diagnosis of infected sinuses in children is more difficult than in adults, because subjective symptoms cannot be expressed. In older children, indefinite pains around the head and face with headache may be complained of, although these symptoms are not always present. The history is very important. It is well to know if the child has had measles, diphtheria, whooping cough and scarlet fever, for White<sup>13</sup> found 32 cases in 50 of his series with infected sinuses who gave a history of childhood diseases. Twenty-nine of these gave a history of whooping cough, 3 had diphtheria, 8 had mumps, while 18 gave a history of chronic colds. Onodi<sup>14</sup> tabulated 23 cases of the earliest reports of infected sinuses in children and all of these were complications of scarlet fever. Any chronic cold with nasal discharge should arouse our suspicion of infection of these structures. Sneezing, headache, irritability and depression are considered very important symptoms by Byfield.<sup>15</sup> Mouth breathing and coughing are also significant signs.

In examination, the nasopharyngoscope is a help, but the procedure is rather difficult. Diagnostic puncture of the antrum with bacteriologic study of the secretion may be resorted to in obscure cases. This procedure has been used successfully by Dean and Armstrong.<sup>16</sup> Transillumination is unreliable, as Skillern<sup>17</sup> points out, and in my own experience has been misleading instead of being of actual diagnostic value. x-Ray examination is our greatest aid, but the plate must be made by a skilful roentgenologist and the interpretation must be correlated with clinical findings. Any child presenting a majority of symptoms mentioned or in any case where there is cause to suspect sinus involvement should certainly have the benefit of an x-ray examination.

During the past few years I have had occasion to see a

number of cases, young children from three to twelve years of age, who have had their tonsils and adenoids removed without their original symptoms of infection clearing up as had been expected. They came in for relief of colds, nasal discharge and mouth breathing. Most of them had had their tonsils and adenoids removed from two to three years previous to this examination. A summary of the important points in the cases presented follows.

### CASE REPORTS

**Case I.**—A. N., aged seven, had tonsils and adenoids removed three years ago in order to clear up persistent nasal discharge. As the result of the operation there was some improvement in the symptoms for a while, but the nasal discharge continued. At the present time there is a great deal of thick mucopurulent discharge in each nostril. A quantity of this drains postnasally causing some pharyngeal irritation. The tonsillar fossae are clean and there are no adenoids. The turbinates are congested and enlarged. x-Ray examination shows clouding of the antra, also some blurring in the ethmoid cells.

**Case II.**—J. M., aged seven and one-half, came for the relief of constant nasal discharge. Tonsils and adenoids were removed two years ago. At the present time there is no tonsillar tissue remaining, no adenoids found. The infection is confined to the nasal cavity. x-Ray examination shows marked clouding of both antra.

**Case III.**—E. G., aged seven. Tonsils and adenoids were removed in 1919. Since operation the patient has had frequent colds and nasal discharge. At the present time there is a great deal of thick mucopurulent postnasal discharge, which produces a great deal of sniffing and coughing. There is no evidence of any remaining tonsil and adenoid tissue. x-Ray examination shows clouding of both antra and some haziness of ethmoids and frontals.

**Case IV.**—I. S., aged ten, had been treated for chronic rhinitis with constant discharge from right nostril. He gave a history of repeated colds. About two and one-half years ago tonsils and adenoids had been removed in an effort to clear up the trouble, but there had been very little relief. Present examination shows a great deal of turgescence of right middle and inferior turbinates. x-Ray examination shows clouding of right antrum. After puncturing the antrum and several irrigations, the infection cleared up and he has since been free of symptoms.

**Case V.**—R. L., aged ten. Patient was referred for investigation of the sinuses as the cause for repeated nasal infections. Two and one-half years ago tonsils and adenoids had been removed but this had little effect on his nasal infection. x-Ray examination shows definite clouding of both antra. There is a great deal of mucopurulent discharge with infiltration of the tur-

binates and mucous membrane. After a simple puncture of the antra and repeated irrigations the infection cleared up.

**Case VI.**—R. L., aged six, had tonsils and adenoids removed three and one-half years ago for relief of repeated colds. Since that time there has been very little improvement in the nasal condition. Examination at this time shows marked hypertrophy of the turbinates with clouding of both antra. This is confirmed by x-ray examination. No remaining tonsil and adenoid tissue was found.

**Case VII.**—R. S., aged thirteen, was referred for investigation for sinuses as a possible cause for repeated attacks of asthma. He has had these attacks since he was a child. They resisted all modern methods of treatment. The diet had been carefully investigated, vaccine had been given, tonsils and adenoids removed, but the symptoms would recur. Nasal examination shows a clouding of the left antrum. After puncturing and irrigating this antrum his local nasal symptoms cleared up and he has had no further asthmatic attacks.

**Case VIII.**—C. H., aged six, for the past three years has had intermittent attacks of asthma. Colds have been frequent and there has been considerable nasal discharge. Tonsils and adenoids were removed and an effort was made to clear up the trouble, but there was little improvement in the symptoms. He was referred for nasal treatment. On examination there was marked clouding of left antrum. The right antrum was small and outlines indistinct. Ethmoids were infected and there was a great deal of enlargement of turbinates.

**Case IX.**—D. L., aged eight, gave a history of repeated colds, a great deal of sneezing and considerable nasal discharge. Tonsils and adenoids had been removed two years previously. Since operation colds have been as frequent, and there has been little improvement in his condition. On examination of the sinuses there was marked clouding of the right antrum. Under local treatment the infection was completely cleared up and the patient has been free from colds for several months.

**Case X.**—F. R., aged fourteen, came for relief of repeated attacks of colds. Tonsils and adenoids were removed six years ago. A great deal of mucopurulent discharge was present in the nasopharynx. Examination of nose showed a chronic ethmoid infection and clouding of both antra. Symptoms completely cleared up under local treatment.

### COMPLICATIONS

Orbital abscess is one of the most frequent, and often the most dangerous complication of accessory sinus disease. A definite abscess is characterized by edema of the affected eye, lids and surrounding tissue. The eyeball is forced out and there is immobility of the extra-ocular muscles. With pus

formation, there is elevation of temperature and increased leukocytosis. If the pressure is not relieved by free drainage, vision may be affected. Some of these cases occur in early life. Case I shows an infant three weeks old with an infected antrum, complicated by orbital abscess. This is an unusual case but it demonstrates the danger of this complication even in young children. Case II is of a child six weeks old, with an infected antrum and orbital complications.

Meningitis and brain abscess is a very serious complication of sinus disease and usually results fatally. Fortunately it does not occur in many cases. The complications associated with any chronic focus of infection may be present with accessory sinus diseases in children. Anemia, loss of weight, low unexplained temperature and gastro-intestinal symptoms are frequently present, so that any such group of symptoms calls for investigation and treatment of the sinuses.

#### TREATMENT

The simple acute infections of the accessory sinuses in children respond very favorably to treatment. Usually small doses of calomel with a few days' rest in bed is all the general treatment required. Locally, the mucous membrane should be kept clean with some warm cleansing spray of normal saline or dilute Dobell's solution, after which some 20 per cent argyrol should be applied. The most convenient way to apply this to the nose is to place the child on his back and with an ordinary eyedropper drop from 15 to 20 drops in each nostril. Most of the cases clear up without complications. In the chronic cases the eradication of the infection is more difficult. If the tonsils and adenoids have not been removed it is advisable to get them out in order to clear up as many foci of infection as possible. Dean and Armstrong<sup>18</sup> found that 80 per cent of their cases cleared up after the tonsils and adenoids had been removed.

Local treatment consists of keeping the infected surface as clean as possible. Suction is very valuable in this condition. for many crevices can be evacuated which could not otherwise be reached. Warm saline sprays are very cleansing, soothing and stimulating to the mucous membrane. After this, it is helpful to make applications of 2 per cent silver nitrate or 20



per cent argyrol. This should be followed by some emollient spray. Young children can be best treated in a hospital. The treatment can be carried out much more satisfactorily if the child is away from its parents. Some cases are helped by the administration of vaccines. A few cases require conservative operative procedures, such as puncture and irrigation of the antra. Only in very exceptional cases is it necessary to do any radical operations.

### SUMMARY

1. All children who have chronic colds with predominant nasal symptoms, such as profuse nasal discharge, stuffiness of the head; mouth breathing and asthmatic attacks, should have a careful investigation of the sinuses.

2. Cases in which tonsils and adenoids have been removed for focal areas of infection, and the symptoms have not cleared up after operation, should be suspected of harboring an infection of the accessory nasal sinuses.

3. Neglected treatment of early infection of the sinuses in children predisposes to chronic infection which may lay the foundation for serious complications in later life.

4. Nasal colds in children should be treated as an important disease. Careful investigation should be made as to their etiology and diagnosis.

5. The proper treatment of infected sinuses in children gives gratifying results. The general health of the patient is improved. They take on weight, develop more rapidly and give every appearance of being greatly benefited. Most of the cases can be cured by local treatment, for only a small number require operative procedures.

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### THE EFFECT OF HEAD INJURY ON THE BEHAVIOR AND PERSONALITY OF CHILDREN: A STUDY OF 20 CASES

#### INTRODUCTION

MUCH has been written on the subject of head injury in children. Ireland<sup>15</sup> who studied 80 children with fractured skulls, covered the literature on that topic quite adequately. Blau,<sup>5</sup> who presents a study of 22 children with mental sequelae following head trauma, also covers the literature on this aspect very thoroughly. In recent books there are excellent discussions of this subject in Kanner's *Child Psychiatry*<sup>16</sup> and Montgomery's chapter in *Practice of Pediatrics*.<sup>20</sup> By far the most complete review of the literature is found in an article by Strauss and Savitsky.<sup>23</sup> It is not the purpose of this paper to duplicate these studies, but primarily to attempt to clarify the question of etiology.

#### PRESENT STUDY

The 20 cases selected for this study comprise all the children who have had head injury and who were seen by the author in the past six years (1931 to 1936 inclusive). In this period the author examined 752 children referred to a child guidance clinic. Eight cases were selected from 232 children seen in the Mental Hygiene Clinic of the Cleveland Board of Education. Twelve cases were selected from 520 children seen in the Baltimore Mental Hygiene Clinic.

There is a marked divergence of opinion among authors as to the incidence of sequelae after head injury. Ireland<sup>15</sup> fol-

lowed his cases for a period averaging thirteen months after skull fracture and found that 11 per cent showed serious sequelae, mostly of a neurologic nature. Beekman<sup>3</sup> made a follow-up study of 331 children with head injury. He found temporary sequelae in 23 per cent but permanent symptoms in less than 5 per cent. These findings are far more encouraging than those of early writers, such as English.<sup>8</sup>

There are no figures exactly comparable to the author's incidence of 2.4 per cent (20 cases in 752 consecutive child guidance clinic children). Kasanin<sup>17</sup> studied 120 children diagnosed as having psychopathic personalities and found that 13 (10.8 per cent) "had serious brain injury during childhood or adolescence." He compared this with a control group of 120 children with different diagnoses. Of these only 2 (1.6 per cent) had had serious brain injury. Healy<sup>11</sup> in a study of 1000 consecutive juvenile delinquents found 21 cases (2.1 per cent) who had suffered a severe head injury. In a later study of 4000 juvenile delinquents Healy<sup>12</sup> found that 3.5 per cent had head injury "with at least a period of unconsciousness." Healy and Bronner<sup>13</sup> in a recent study of 105 delinquents compared with 105 nondelinquent siblings, found a history of severe head injury in 4.7 per cent of the delinquent group and none in the control group.

The author used two criteria for selecting the cases. First, at least two of Kennedy's<sup>18</sup> criteria of severe head injury were satisfied. This resulted in a group of 10 such cases. Second, the child had a mild degree of head injury (scalp laceration or a short period of unconsciousness) on which a parent blamed the child's difficulty. This resulted in a group of 10 cases with a mild degree of injury. It is of interest to note that in only 3 of the 20 cases neither parent blamed the accident for the children's difficulty, and all 3 cases fell in the group with severe injury. In 7 cases (3 of them mild) the parents attempted to sue or did collect money because of the injury.

In describing the group as a whole it is interesting to note that there were 19 boys and 1 girl. In Blau's<sup>5</sup> study of 22 children, 20 were boys. The children ranged in age from six to seventeen years, with the average age about ten and one-half years. They were seen from one month to nine years after the accident. The average interval of time was about

five and one-half years. The group was nearly average in intelligence. Their intelligence quotients (I. Q.), based on the Stanford-Binet test, ranged from 56 to 108. The average was about 89. The group as a whole averaged 2 semesters retarded according to chronological age (ranging from 2 semesters accelerated to 8 semesters retarded). They averaged at grade, however, according to Stanford-Binet mental age (ranging from 4 semesters accelerated to 4 semesters retarded). The brighter children tended to be retarded while the duller ones were accelerated, according to mental age.

### BEHAVIOR AND PERSONALITY

The most characteristic statement regarding children who have suffered from brain injury is that there is a change of character following the trauma. Beekman<sup>3</sup> describes a wide variety of symptoms. He writes, "The symptoms complained of in the sequelae are more often of a subjective or emotional type than those of an objective type. Headache is the commonest complaint and it usually clears up within a year after the accident. Emotional instability is seen frequently. This varies anywhere from mild nervousness to a behaviorism which is a total change from the child's former character. . . . The severity of this change in behavior varied from mild emotional symptoms—'nervousness,' attacks of crying for no apparent cause or slight irritability—to a change in character, where the child became sullen, quarrelsome and incorrigible." Most authors describe explosive outbreaks of temper, with destructive, cruel behavior. Meyer,<sup>10</sup> in an early study of head injury in adult mental patients, called this the "type with explosive diathesis." Healy<sup>11</sup> describes this reaction thus, "The mental changes typically lead to passionate outbreaks and great decrease in the power of self-control and an easy mental fatigability creates lack of continuity of purpose." Strecker and Ebaugh<sup>24</sup> studied 30 children in a psychiatric clinic, who gave a previous history of head injury. Fifteen (50 per cent) showed these explosive outbreaks of temper. Blau<sup>5</sup> calls this reaction chronic posttraumatic behavior disorder and describes them as "asocial, unmanageable and unyielding to any form of training." Of his 22 cases 12 (54 per cent) showed

this behavior. Blau,<sup>5</sup> Kasanin,<sup>17</sup> and Strecker and Ebaugh,<sup>24</sup> point out the similarity of this mental picture with that seen in children after epidemic encephalitis. Bond and Partridge,<sup>6</sup> describing postencephalitic behavior disorders in children, write, "We have found evidence that nothing quite matches it except possibly the traumatic disorders."

Blau<sup>5</sup> classified his 22 cases into four groups, with some overlapping, which accounts for discrepancies in totals and percentages. Six of his cases (27 per cent) showed acute psychoses. Blau states that he can find no reference in the literature to this reaction in children. Twelve of his cases (54 per cent) showed chronic behavior disorders. Five (22 per cent) showed posttraumatic epilepsy. Two (9 per cent) showed cerebral defect and intellectual retardation.

In the present study an attempt was made to classify the cases according to the behavior of the child following the injury. This was difficult as some cases overlapped, that is, they showed behavior of more than one type. This overlapping will account for discrepancies in totals and percentages. In this group there were no cases showing epilepsy or acute psychosis as sequelae.

#### CHILDREN SHOWING NEUROTIC SYMPTOMS

This was by far the largest group in the present series, consisting of 10 cases (50 per cent). The most frequent symptoms found in this group were: "nervousness," 8; headache, 4; enuresis, 4; having many fears, 4; nail biting, 3, and sleep disturbances, 3. The following case is presented to illustrate this type of reaction.

*Case I.—Reason for Referral.*—M. R., a six-year-old white girl, in kindergarten, was referred in November, 1936, to the clinic, two years after her accident. She has many fears and does not play with other children.

*Development.*—Oldest of three children. Birth and development were normal. She was hospitalized a few days

*Diagnosis.*—Gastro-intestinal disorder, erythema multiforme. Six months later she had a discharging ear

*Accident.*—At the age of three years and ten months patient fell from a porch, striking her head on the ground. She vomited for two successive days. She was hospitalized for twelve days. The hospital reports negative findings on a careful neurologic examination. x-Ray of the skull showed a

fracture of the left parietal and temporal bones with no displacement or depression. No spinal puncture was performed. Recovery uneventful.

*Recent Behavior.*—Mother blames most of patient's recent trouble on the accident. Since the accident patient has been nervous, fearful, timid, biting her nails. She cries easily, is afraid of the dark and is frightened by the least noise. She is especially afraid if children (even younger) show any aggression toward her. Thus she is afraid of her three and one-half-year-old half-brother. She has had occasional enuresis. She won't eat unless her mother urges her.

*Home Environment.*—The mother, Protestant, came from an unhappy, broken home. All her brothers and sisters have been divorced. Mother married a Catholic at sixteen years, because the man threatened to kill her if she didn't marry him. She left her husband because he drank so much. She then lived with patient's father but left him when he went with women. She returned to her husband but plans to leave as he still drinks and goes with women.

When drunk he throws up to mother the fact that patient is not his child. Mother induced abortion twice and her husband has been disgusted with her because of this. Patient is afraid of her stepfather when he comes home drunk. During much of this time patient lived with her maternal grandmother.

*Examinations.*—*Physical.*—Several examinations following the accident have been essentially negative.

*Psychologic.*—Stanford-Binet: chronologic age, six years one month; mental age, five years four months; I. Q., 84. Tests ranged from three to seven years.

*Rating.*—Dull normal intelligence.

*Psychiatric.*—Patient describes how her father left after a fight with mother and how mother is trying to force him to buy clothes for patient. Patient is very unhappy with stepfather. He comes home drunk and fights mother and beats patient. Patient is afraid of him. He tells mother he won't keep patient, she will have to leave. Patient wishes she could live with some relative and describes vague fears of men assaulting her.

*Interpretation.*—The patient feels extremely insecure. She is illegitimate, is rejected by her mother, and has moved about a lot among relatives. She is afraid of her stepfather and is extremely unhappy at home. These factors are more important than the head injury in producing her symptoms. The mother needs to use the head injury as a form of alibi.

*Treatment.*—The clinic suggested that patient be placed either with some relatives or in a foster home. As a way of achieving that it was suggested that she first be placed in the children's convalescent school. This has been done and patient has already (two weeks) shown definite improvement.

This neurotic reaction is also illustrated by Cases VI, VII, VIII and IX in the Appendix. Half of this group of 10 cases showed severe head injury. In 8 cases a parent blamed the child's trouble on the injury. In only one instance, however, did a parent attempt to sue for damages.

## CHILDREN SHOWING DELINQUENT BEHAVIOR

This group contained 5 cases (25 per cent). The most frequent symptoms found in this group were: defying authority, 4; stealing, 3; truancy, 3, and running from home, 2. Of these children 3 had been in juvenile court and one in an institution. The following case is presented to illustrate this reaction.

*Case II.—Reason for Referral.*—E. H., a twelve-year-old white boy, in low fifth grade, was referred in January, 1931, to the Cleveland clinic seven years after his accident. He steals from parked cars and gets into a lot of mischief such as riding cars, pulling trolleys off street cars.

*Development.*—Youngest of 4 children. Birth was unwelcome to both parents. Mother was very ill during pregnancy and unhappy because she hated living with her mother-in-law. Birth was prolonged, a breech delivery. Patient was breast-fed three months. In telling this mother explained, "It wasn't because I didn't want to give it to him." Development was retarded. Walked at fourteen months and talked at two years. First teeth came at ten months. Patient had chickenpox severely at three years. Patient had tonsillitis every winter and had coughs lasting most of the winter. Has always been underweight. Mother babies him—won't let him go swimming. She said, "He's my baby and I like to fondle him a lot." Patient slept with mother until he was six years old.

*Accident.*—At five years of age patient was hit by a truck and was unconscious for nine days. He was in the hospital twenty-three days and they diagnosed a transverse, frontal fracture of the skull.

*Recent Behavior.*—Mother claims that ever since his accident patient has been sneaky. He goes with a gang of boys who steal. On two occasions patient was taken to Juvenile Court for stealing. He smokes a great deal. He fights with boys. At school he tries to attract attention. His school work is careless.

*Home Environment.*—Both parents were brought up in unhappy homes. Their parents quarreled, were abusive and separated. Both parents are extremely immature and neurotic. Both parents have had nervous breakdowns. The father has some almost psychotic symptoms. The mother had two nervous breakdowns. Both parents were very disappointed in their marriage. The father deserted for three months before patient's birth. Neither parent wanted any children. For this reason the mother induced abortion many times. She never liked housework and neglected her children.

*Examinations—Physical*—He is 12 per cent underweight, has diseased tonsils, cervical adenitis and thickened ear drums.

*Psychologic*—At eleven years of age patient was given the National Intelligence Test and obtained an I. Q. of 68.

*Stanford-Binet*—Chronologic age, twelve years one month; mental age, eight years two months; I Q. 67.

*Rating.*—Borderline mental defective.



*Psychiatric.*—Patient shows a marked degree of attachment to and dependence on his mother, and hostility toward his father. Says he is his mother's favorite while his father picks on him all the time. He will never marry till his mother dies. Is very anxious to learn to dance so he can dance with his mother before she is too old. He shows a marked degree of feelings of inferiority and relates these to his accident. Since his accident he has never been strong and has been sick a lot. He can't play baseball. Tells how he likes to do stunts and show off. He talked frankly about his stealing.

*Treatment.*—Tonsillectomy was advised. Also placement in a special class for retarded children. The school was asked to help patient build up his self-confidence. The mother was asked to give patient more recreational freedom. Patient was seen several times by the psychiatrist in treatment interviews. During the period of treatment (six months) patient showed definite improvement with no evidence of stealing.

This delinquent behavior is also illustrated by Cases X and XI in the Appendix. Two of this group of 5 cases showed severe head injury. In all 5 cases a parent blamed the child's trouble on the injury. In 2 cases a parent attempted to sue for damages.

#### CHILDREN SHOWING EXPLOSIVE TANTRUMS

This group contained 4 cases (20 per cent). The most frequent symptoms found in this group were: severe, explosive tantrums, 4; attacking adults or children, 4; marked hyperactivity, 2; being unmanageable, 2, and attention-getting behavior, 2. The following case is presented to illustrate this reaction.

*Case III.—Reason for Referral.*—G. C., a six-year-old white boy in high first grade, was referred in September, 1934, to the clinic, two months after his accident. Ever since his accident he has had severe temper tantrums. Parents think he is mentally deranged.

*Development.*—Fourth of 5 children. Birth and development normal. Breast-fed over a year. At first mother claimed he was an easy child to manage and normal until his accident. In a later interview she said patient has always had nocturnal and diurnal enuresis. He has always been nervous and hyperactive. Physicians have treated him for nervousness and one doctor diagnosed chorea. When four years old patient fell off a wagon and bumped his head. He was unconscious and vomited when he woke up. Mother was frantic then and dates his nervousness from the first fall.

*Accident.*—See above for accident at four years. At six years seven months of age patient was hit by an auto. Immediately after the accident patient became so "wild" it took 4 men to get him into a truck which took him to the hospital. The hospital diagnosed concussion and lacerations of head

and shoulder. At the hospital he was unconscious for half a day and in a daze for two days. He was in the hospital three weeks.

*Recent Behavior.*—At first mother claimed that all of patient's trouble was since the last accident. Later she admitted difficulties before it (see above). Since patient's return from the hospital he has had violent temper spells three and four times a day. These occur when he can't have his way. In these he throws himself on the floor and screams, or he attacks his mother or brothers. The school does not complain about his behavior. The mother fears a clot has formed on the brain and she fears he will go crazy, have epilepsy or die. The father fears patient will kill someone. Mother is asking agencies how she can sue for compensation.

*Home Environment.*—The father had nocturnal enuresis till late. He always disliked school. He is somewhat shiftless and did not support his family well even before the depression. He has been on relief most of the depression. The mother is a dull, ignorant person who is extremely upset over patient's condition. Mother's fears are augmented by the fact that one of her children died at the age of one year following a fall.

*Examinations.*—Physical and neurologic examinations were essentially negative.

*Psychologic.*—Stanford-Binet: chronologic age, six years nine months; mental age, six years two months; I. Q., 91. Tests ranged from five to nine years.

*Rating.*—Average intelligence.

On 3 performance (manual) tests he gave an average performance. At the end of the test he suddenly burst out crying and ran to his mother.

*Psychiatric.*—Patient was extremely resistive and cried most of the time. He said his mother was afraid to bring him to the clinic for fear we might do something to him. Also his mother won't let him go to school because she is afraid—he doesn't know why.

*Interpretation.*—The patient may have suffered from brain injury resulting in increased irritability but it is felt that the major part of his difficulty is based on his mother's extreme anxiety regarding patient. Patient reflects this by feeling marked anxiety himself.

*Treatment.*—Patient was sent to a children's convalescent school with the recommendation that he remain six months. He improved so markedly that he was sent home after two months. His improvement lasted only two or three weeks after his return home. Treatment at the clinic was suggested but mother has consistently broken appointments.

This tantrum behavior is also illustrated by Cases XII and XIII in the Appendix. Only one of this group of 4 cases showed severe head injury. In 3 cases a parent blamed the child's trouble on the injury. In 3 cases a parent attempted to sue for damages.

## CHILDREN SHOWING MENTAL RETARDATION

This group contained 5 cases (25 per cent). The symptoms complained of were: poor school progress (or failing work), 5; inability to learn, 2; reading disability, 2. Four of this group of 5 cases showed severe head injury. In 4 cases a parent blamed the child's retardation on the injury, and in 2 cases a parent attempted to sue for damages.

Blau<sup>5</sup> presents 2 cases of mental deterioration following head injury. Strecker and Ebaugh<sup>24</sup> present 6 cases and Healy<sup>11</sup> presents 1 case. In all these cases, as well as those in the present study, mental efficiency was impaired as evidenced by poor school work. However, the evidence for an actual change in mental ability is far from convincing. This point cannot be settled until more cases are reported where a child was given psychological tests before and after the head injury. The author was able to find in the literature only one report of a child who had been tested before and after a head injury. Hardwick<sup>10</sup> describes a fourteen-year-old boy who was given the Stanford-Binet test before and after a severe head injury. She did not give the results but writes, "In general his reactions were slower but more accurate than before."

In the present study the average tested intelligence of these 5 children (I. Q., 87) was practically the same as the average for the entire group (I. Q., 89). All of the children in the present study were given the Stanford-Binet test after the head injury. Three of these had been given the same test before the head injury. Thus Case IV (below) was tested twelve months before his head injury and received an I. Q. of 79. On the test given eight months after the accident the I. Q. was 74. Case XII (Appendix) was tested three years before his head injury and obtained an I. Q. of 97. When tested fourteen months after the accident his I. Q. was 97. Case V (below) was tested three years before his head injury and received an I. Q. of 97. On the test eighteen months after his accident the I. Q. was 99.

In these 3 cases the two tests, given before and after the head injury, were as close to each other as Stanford-Binet results can be expected to be when repeated on the same individual. Two of these 3 cases received severe head injuries,

and in all 3 cases a parent attempted to sue for damages. The following case is presented to illustrate this situation.

**Case IV.—Reason for Referral.**—C. G., a twelve-year-old white boy, in opportunity class, was referred in May, 1936, to the clinic six months after his accident. Ever since the accident he has been nervous, suffering from headaches, and his school work has become worse.

**Development.**—The eighth of 9 children. Birth and development were normal (according to the father). At eight and one-half years he had an appendectomy. Father says that up to the accident he was a happy, typical boy, doing well in school, playing well with other children. In contrast to this the school said that before the accident the patient had failed so much (at nine years he was in low third grade and doing only first and second grade work), they gave him a Binet test and put him in the opportunity class (for dull children) one year before the accident.

**Accident.**—At eleven and one-half years patient fell down a 14-foot embankment, onto concrete, injuring his leg and head. He was unconscious for two hours. When he came to, he vomited and was dizzy. He was taken to a physician's office. The father quotes the physician as saying that patient suffered from a "permanent nerve injury." Father is suing the owner of the property for \$15,000.

**Recent Behavior.**—Father claims that the accident affected the boy's mind (making him feeble-minded), and his nerves—he has headaches, gets "shaky spells" and bites his nails. Also patient has pains in his legs and his back. Father also claims that patient's spine has become crooked. Evidence from the school indicates that patient's school work has not become worse since the accident.

**Home Environment.**—The father is a rather dull man who never kept a job long. Three years ago he injured his head in an accident. He sued and was awarded \$1000 which has not been collected.

Since then he has been on relief on an occasional Federal job. The mother had little education. Was fourteen years old when she married. Bearing 9 children and 3 operations for gallbladder trouble have kept her ill a great deal. The oldest son was in an accident. The father sued and collected \$171. The second son has tuberculosis. The third son was in an accident at nine years which left him "mentally defective." The father sued and collected \$200. This boy finished the sixth grade at sixteen years. The father tried to get him into the school for the feeble-minded but the school refused to accept him.

**Examinations.—Psychologic.—School tests** (given twelve months before the accident).

Stanford-Binet: chronologic age, nine years eight months; mental age, seven years eight months; I. Q., 79. Tests ranged from six years to nine years.

At nine years eleven months he was given a reading test and scored at low first grade.

At ten years six months he was given arithmetic test and scored at low second grade.

**Clinic Test** (Given Eight Months After the Accident).—Stanford-Binet:

chronologic age, twelve years two months; mental age, nine years; I. Q., 74. Passed all of the nine-year tests and none of the ten-year (or above).

*Rating.*—Very dull intelligence.

Rogers Test of Personality Adjustment showed a high degree of maladjustment in every category but a particularly high "social maladjustment."

*Psychiatric.*—Patient said his mother worried most about his accident and fears he'll get in another. Father "just scolded me for being so careless." Father beats patient if he gets poor marks in school. Both parents threaten patient with reform school. Father fears patient will shoot someone. Mother makes the children behave by threatening them with the devil. Patient often dreams he is falling. Also dreams someone chops his mother's head off. Patient dislikes opportunity class and wants to go through college.

*Interpretation.*—Patient's present symptoms may partly be due to brain injury but they are aggravated by his mother's anxiety and his father's tendency to sue about all accidents. Patient's school achievement is handicapped by his dullness, but especially by his father's educational drive and his dislike for special education. This is based on father's need to prove that patient's dullness is due to an accident.

*Treatment.*—The psychiatrist interviewed the father urging him to drop the suit since the parents' continued anxiety was making patient more nervous. An attempt was made to get father to accept special education for patient, leading to trade training for semiskilled work. It was recently learned that the father did drop the suit and the patient has improved.

A similar situation is illustrated by Case XIV in the Appendix.

One case (V below) would not fit in any of the categories described above. This boy had a severe head injury while being treated at the clinic. Before the accident his behavior was somewhat similar to the children described above as showing "explosive tantrums." However, he improved under treatment and continued improving in spite of his accident. The report of this case follows:

*Case V.—Reason for Referral.*—G. G., a seven-year-old white boy, in low second grade, was referred in December, 1932, to the clinic, three years before his accident. He stole, was hyperactive, disobedient, destructive and unmanageable.

*Development.*—Third of 4 children. Birth and development were normal. Has always had nocturnal enuresis until seven years of age. Has always been nervous, hyperactive, mischievous and annoying. The school reported his behavior as "explosive." Patient is annoying in class and unpopular with children. Constant attention-getting behavior.

*Accident.*—(See below.)

*Home Environment.*—The mother was brought up in a miserable home. None of her children were wanted and she was unable to control them,

especially the boys. She was a religious fanatic. The *father* was always very serious and good in contrast to his father, who was a drunkard. He is a religious fanatic and is very intolerant of any misbehavior by his boys. They show the four traits he loathes the most—lying, stealing, cruelty and obscenity. He punishes them severely and adds that God will punish them too. Mother died when patient was six years old. After mother's death all 4 children were placed in boarding homes until father remarried two years later. *Patient* was in two boarding homes. Although he improved, the boarding mother felt he was so hopeless she asked that he be removed from her home. All the children went home four days after father remarried. The *stepmother* is also a religious fanatic who is very intolerant. Thus going to movies is a sin. She had a nervous breakdown prior to her marriage and was ill a year. She had no control over patient at all.

*Examinations.—Physical.*—Findings were essentially negative.

*Psychologic.*—(Tested three years before his accident.) Stanford-Binet: chronologic age, seven years three months; mental age, seven years; I. Q., 97. Tests ranged from five to nine years.

*Rating.*—Average intelligence.

Scores on three performance tests were average.

(Tested one and one-half years after the accident.) Stanford-Binet: chronologic age, eleven years eight months; mental age, eleven years seven months; I. Q., 99. Tests ranged from nine to sixteen years.

*Psychiatric.*—Patient shows many signs of feeling very insecure. He has been told that his swearing and stealing made his mother die. He describes his father and stepmother as very punishing and repressive and says he was happier in his foster home. He frequently mentions the things he does as sins. "God doesn't want children to go to the movies."

*Treatment.*—As both father and stepmother were unable to control patient, and as he was getting steadily worse in his behavior it was recommended that he be placed in a foster home, preferably in the country.

*Patient was placed* on a farm home at eight and one-half years of age (five months after his father remarried). The patient has been in that home for three years (1934 to 1937) and his behavior has improved steadily. He has made steady progress in school. At eleven years he is in the fifth grade and doing passing work. He has been brought to the city occasionally to visit his home and to be seen by the psychiatrist. After he was in this home one and one-half years he received his *head injury* (see below). The psychiatrist resisted attempts by the father to sue, to have a court trial and to have the boy brought home. Psychiatrist insisted on patient being sent back to the same foster home and no more attention be paid him than if he broke a leg. In the one and one-half years since the accident patient's progress has continued so that his stepmother said "The accident knocked the badness out of him."

*Accident*—At ten years, while in a foster home under clinic and agency treatment, patient was hit by a truck. Patient was unconscious a few minutes and later at the hospital became unconscious again. x-Ray showed a "circular fracture in the right temporal region. There is no evidence of depression." Patient was operated on the day of admission. A large bony plate was lifted

Extradural hemorrhage was found. Clots were removed, vessels ligated and bone flap replaced. A later x-ray showed the bone flap in good position and no evidence of depression. Patient made an excellent recovery and was discharged after three weeks.

### ETIOLOGY

In psychiatry the study of etiology is more complex than in most other branches of medicine. In 1936 the author wrote,<sup>22</sup> "Any attempt to study the etiology of behavior or personality traits is beset with seemingly insurmountable obstacles owing to the complexity of the problem. The variable and uncontrolled factors are so numerous that proof of a cause and effect relationship is nearly impossible. . . . A relatively recent, and widely accepted, theory has made the study of etiology even more confusing. This Theory of Multiple Etiology states that every behavior or personality trait is the result of many causal factors. This theory has two corollaries. One states that any trait, such as shyness, is caused by different sets of factors in different individuals. The other states that shyness in any individual is the result of many causal factors."

There is a strong tendency among medical men to resist this concept. They wish to simplify their thinking. Thus psychiatrists sometimes find it difficult to persuade general practitioners that a patient may have a serious organic condition (such as heart disease or tuberculosis) and a psychoneurosis at the same time. The tendency is to insist that the symptom is either due to organic or psychogenic factors, but not to both in the same individual.

Regarding head injuries, a few writers stress the organic factor of brain damage. Friedman<sup>9</sup> cautions us as follows: "On the basis of accumulating experience, we may say that, at least in some of the cases of 'traumatic neurosis,' definite organic changes that can be visualized in the encephalogram have been brought to light." Also Blau,<sup>5</sup> in discussing the 12 children with posttraumatic chronic behavior disorder, writes, "The principal interest in the post-traumatic behavior disorder in children lies in the fact that although it resembles a psychopathic personality reaction of psychogenic etiology, it is nevertheless definitely of organic origin and is probably caused by a localized lesion of the brain."

Some writers stress the factor of constitution or heredity. Thus Healy<sup>11</sup> writes, "Other possible causes are also nearly always in the background. Often we have gained evidence of a prior neuropathic constitution, or of some grave defect in heredity. Except in a case of arrested development, we can fairly say we have never been able to discern traumatism as the sole assignable factor."

Although some authors stress the functional or psychogenic aspects, most of them point out the necessity of considering both organic and functional factors in these cases. Thus Meyer<sup>19</sup> in 1904 wrote, "Looking over our cases etiologically, we cannot fail to be impressed by the concurrence of several etiological factors in the greater majority." Strauss and Savitsky<sup>23</sup> cite Babinski<sup>1</sup> as being one of the first to emphasize the frequency with which organic and functional disease can occur in the same patient. Strauss and Savitsky<sup>23</sup> agree that this concurrence exists. They write, "Such psychogenic superimposition is much more common than is usually admitted. . . . It is necessary for once to abandon the specious dichotomy, organic and psychogenic, in an approach to cases of head injury. In most cases there is a subtle interaction of psychic and organic factors. A case is not either organic or functional." Regarding etiology Strecker and Ebaugh<sup>24</sup> write, "The findings should lead to caution in referring these conditions to hypothetical molecular changes in the brain. We should prefer to think of the problem in terms of the total reactions of the individual child. A study of the child, the situation and the environment, and the reaction to this situation before and after the injury is therefore imperative." Kasanin<sup>17</sup> minimizes the specific effect of brain damage. He writes, "It seems to me that severe brain injury and encephalitis as such do not cause a specific reaction in the individual so far as his behavior patterns are concerned. It appears that any factor which causes a diffuse process in the central nervous system will interfere with the formation of proper inhibitory influences and will greatly hinder the complete integration of the individual's behavior."

Stressing functional factors, Kasanin<sup>17</sup> writes, "It is very frequent that the overzealous and anxious parents focus the attention of the child upon the injury and the clinical picture



then may be entirely due to functional factors." Barraclough<sup>2</sup> studied the behavior and personality of children following various illnesses, including head injury. He stresses the factor of emotional handling by parents. Bender,<sup>4</sup> in an article in which she describes a relationship between encephalitis and head traumas in children, and psychopathic personality, writes, "Of great interest is the fact that personality deviations as severe as any of these we have described may develop in a child who has had no birth injury, skull fracture or encephalitis but who has been deprived of the normal family-social life at the critical period in life, which is the preschool age, when his personality is maturing. As a result we find disturbances in the integration of the maturation patterns of the brain as serious as though the injury were a structural one. . . . Such a child is always emotionally infantile, always craving the love of the mother it never had and is insatiable in his demands for attention, grasping and clinging psychically. He is restless and has marked hyperkineses. His instability as he grows older will show criminal or psychotic episodes. Neurological deviations are usually absent but motility mannerisms may so closely resemble them that at times they are confusing to the examiner."

In the present series of cases a study was made of the functional, psychogenic or environmental factors that may have an etiological bearing. The results of this study are presented in Table 1.

The commonest finding, parental anxiety, is seen most frequently in mothers. It is a common observation that parents tend to blame a fall in infancy for difficulties their children show later. Parents need to project the origin of their child's maladjustment onto some cause, such as head injury, in order to protect themselves from being considered responsible. A certain amount of maternal anxiety is normal. It seems nearly always to be exaggerated when the injury is to the head. Thus a broken leg produces only a small fraction of the emotional response brought out by a fractured skull. The head represents a sort of magic zone, with a large number of superstitions regarding injury in that area. Similar clinical pictures are sometimes seen in children who have had birth injuries. Physicians have warned the mothers that the children would be

TABLE 1

PSYCHOGENIC AND SITUATIONAL ETIOLOGIC FACTORS (20 Cases)

Factor.	Mothers.	Fathers.	Total.	
	Number of cases.	Number of cases.	Number of cases.	Percent-age.
1. Parent shows extreme anxiety regarding patient.	15	2	16	80
2. Parent rejects patient.	12	8	15	75
3. Parent is extremely unstable or neurotic.	11	11	14	70
4. Home is broken.	..	..	7	35
5. Parent attempted to sue for damages.	..	..	7	35
6. Patient shows marked feeling of insecurity.	..	..	6	30
7. Parent puts a great deal of educational pressure on patient.	3	3	4	20

nervous. This has resulted in intensifying the mother's normal anxiety. The findings of the present study indicate that the child's behavior correlates more closely with the intensity of the parent's emotional response, and less closely with the severity of the injury.

The next most frequent factor is the rejection by one or both parents, most frequently the mother. The author reported a study of this factor in two papers.<sup>21, 22</sup> In the first paper<sup>21</sup> the author wrote, "The study shows that maternal rejection is primarily due to the mother's unhappy adjustment to marriage. This in turn is usually a result of immaturity and emotional instability on the part of one or both parents. These mothers express their rejection by undisguised forms of neglect and cruelty, by overprotection as a reaction to feelings of guilt, or by an inconsistency of handling, characterized by a mixture of these two methods. The children in turn, suffer from an unstable environment and inconsistent handling. Feeling more insecure than the average child, they are im-

pelled by the necessity of extracting from their parents and other adults expressions of being welcome or important. Thus they are peculiarly sensitive to attention. They derive a certain satisfaction from having their mothers upset about them and much of their specific behavior represents a discovery on their part of what their mothers fear the most. Finally, this study supports the conclusion that maternal rejection is an important factor underlying the insecurity which so often accompanies the clinical picture of emotional instability." In this respect the cases of the present study are somewhat similar in their clinical pictures to the cases of rejection studied. Thus in both studies there was a high per cent of broken homes (36 and 35 per cent), one or both parents are extremely unstable or neurotic (60 and 70 per cent) and the patients feel insecure. The main difference in the groups is the finding in the present study of head injury and the extreme emotional response of parents to this injury.

#### PROGNOSIS

Most writers are quite pessimistic regarding the prognosis of behavior disorders in children following head injury. Kasanin<sup>17</sup> concluded that the prognosis was poor, but not so poor as that seen in children following epidemic encephalitis. Healy *et al.*<sup>14</sup> feel that the prognosis for delinquents showing "traumatic constitution" is relatively poor. Strecker and Ebaugh<sup>24</sup> studied 30 children showing behavior changes following head injury. They state that 6 (20 per cent) are improving but the outlook for 24 (80 per cent) is discouraging. Beekman<sup>3</sup> studied 19 children showing behavior changes following head injury. He gives a more encouraging prognosis. He writes, "Ten children (52 per cent) recovered entirely, 6 (31 per cent) were much improved, but in 3 (16 per cent) no change was noted." He feels that there is a relation between the severity of the injury and the seriousness of the behavior disorder. The present study does not bear this out. Baraclough<sup>2</sup> also disagrees with Beekman. He writes, "The degree of severity of the initiating illness or accident bears no relation whatsoever to the behavior change for which it is blamed. Most trivial accidents and minor illnesses are frequently accepted as being responsible for symptoms that appear."

In the present study 4 cases (20 per cent) showed marked improvement and 9 cases (45 per cent) showed slight improvement under treatment. Four cases (20 per cent) showed no improvement and three (15 per cent) showed only temporary improvement. The relationship of these findings and treatment methods will be discussed later.

### TREATMENT

Regarding treatment, most authors agree on the value of a change of environment. In Healy's early study<sup>11</sup> he advocates a quiet rural life and stresses the avoidance of alcohol and overheating. In a more recent study Healy *et al.*<sup>14</sup> again advocate rural placement or "the steady regime of small semi-disciplinary schools." Regarding treatment Beekman<sup>3</sup> writes, "Care, isolation from emotional excitement and training quickly showed their effects on these children's behavior." Kasanin<sup>17</sup> writes, "It seems to me that in as much as any form of organic treatment is impossible in these cases, the only method of treatment is environmental change and psychotherapy." He feels that if usual methods fail, correctional institutions should be used for the training of the child and the protection of society.

Strecker and Ebaugh<sup>24</sup> discuss treatment thus, "Rest from physical and mental exertion, removal to a quiet, nonirritating environment, intensive study in mental hospitals, more individual consideration in school, special classes and vocational guidance, are all matters of importance in treatment. . . . During periods of mental excitement, we find that drugs are of little avail, but hydrotherapy is often helpful."

In the present study an attempt was made to correlate the treatment methods used with the results obtained. This is shown in Table 2. It will be seen from this that the best results were obtained by psychotherapy with the patient directly, and advice given to parents regarding methods of handling the child. In this advice the author urges parents to treat the child more as a normal child and to drop damage suits. The need to sue for damages affects the child indirectly by prolonging the emotional attitude of the parents. In the author's opinion the harm done by this attitude far outweighs the benefits derived by bringing suit for damages.

TABLE 2

## TREATMENT METHODS AND RESULTS (20 Cases)

Treatment methods.	Totals.	Results.				
		Marked improve- ment.	Slight improve- ment.	Tem- porary improve- ment.	No improve- ment.	Results unknown
		4	9	3	2	2
1. Psychotherapy of patient plus advice to parent.	5	3	2			
2. Advice to parent only.	3	...	3			
3. Psychotherapy of patient only.	1	...	1			
4. Tutoring of patient only.	2	...	2			
5. Psychotherapy of patient plus tutoring.	1	...	1			
6. Psychotherapy of patient recommended but not carried out.	2	...	...	...	2	
7. Placement in foster home.	1	1				
8. Placement in institution (short period).	3	...	...	3		
9. Placement in institution (long period)	1	...	...	...	...	1
10. Psychotherapy in home city recommended.	1	...	...	...	...	1

In some instances tutoring in specific subjects was beneficial to the child. Placement of the child in a well-run institution results in temporary improvement, but in each case the child resumed his former behavior difficulties soon after he returned home. The author feels that more prolonged treatment in a mental hospital equipped to care for children is indicated in many of these cases. Some of these children would profit by the hospital treatment designed for encephalitics and described by Bond and Appel.<sup>7</sup> They describe an experience similar to that seen in this study. They write, "Forty-six of forty-eight postencephalitic children improved while at the hospital." A follow-up study of a group sent home showed that over half made doubtful adjustments or became worse. On the other hand 45 per cent made good social adjustments. Most states lack facilities for the hospital treatment of children showing serious behavior disorders following encephalitis or head trauma.

## CONCLUSIONS

1. A study is presented of 20 children seen in a child guidance clinic who showed behavior or personality disturbances following head injury.

2. Half of the children suffered from severe head injury. In all of the cases where the injury was of a mild degree the parents blamed the injury for the disturbances shown.

3. The behavior and personality disturbances were classified, with some overlapping, as follows:

I. Children showing neurotic symptoms.....	10 cases
II. Children showing delinquent behavior .	5 cases
III. Children showing explosive tantrums . . . . .	4 cases
IV. Children showing mental retardation .	5 cases

4. The mental retardation was found to be more functional than actual. The children did poorly in school, but no deterioration could be detected by psychological tests.

5. Three cases are presented who were given the Stanford-Binet test before and after their head injury. In each case the results were nearly identical.

6. In studying etiology the necessity is stressed of considering organic and psychogenic factors as operating at the same time.

7. The effect of organic brain injury seems to be a diffuse increase of irritability with a general decrease of inhibitory functions. The effect of brain injury on behavior and personality is in no sense specific.

8. There is little correlation between the type of severity of the change in the child's behavior with the severity of the head injury.

9. There is a greater correlation between the behavior change and the emotional attitude of the parents toward the injury. These parental attitudes become important etiologic factors of a psychogenic or situational type.

10. The commonest situational factors were attitudes of extreme anxiety on the part of the parents and extremely unstable home situations. The parents were frequently unstable, neurotic and rejecting and the homes were frequently broken.

11. The prognosis is not so poor as some authors have described. In the present series 4 cases showed marked improve-

ment under treatment, 9 cases showed slight improvement, while the rest showed none or only temporary improvement.

12. The most effective therapy was found to be direct psychiatric treatment of the child combined with advice to parents regarding methods of handling the child. In this advice parents are urged to drop damage suits and to treat the patient more as a normal child.

13. Placement in institutions of a nondisciplinary type benefits some of these cases but the effects are temporary unless the placement can be arranged for a prolonged period and the child treated psychiatrically. Only a few states have children's wards in mental hospitals where the cases with severe behavior disturbances can be adequately treated.

#### APPENDIX

*Case VI.—Reason for Referral.*—H. N., a nine-year-old white boy, in second grade, was referred in November, 1933, to the clinic, four years after his accident, because of poor school progress since his accident. He has nocturnal and diurnal enuresis. "He can't learn. He forgets so easily."

*Development.*—First of 3 children. Birth full term, breech delivery with instruments. Never breast-fed as mother's milk was not suitable. Pneumonia at nine months. Talked at ten months. Walked at fourteen months. Mother said he has always been nervous and has always wet the bed.

*Accident.*—At five years ten months patient was hit by an auto. Was unconscious ten minutes, vomited, became drowsy, cried and trembled. Was semicomatose for some time and examined thus. Had many lacerations and contusions over the scalp. Eyes deviated to the left. Liver edge felt. Abdominal reflexes absent. Babinski and Oppenheim reflexes positive bilaterally. Right pupil more active than left. Pulse 114 to 102. Temperature around 100° F. for several days. Blood pressure, 100/50 to 118/80. x-Ray showed fracture of right clavicle and "questionable fracture of skull." No spinal fluid taken. Diagnosis: concussion of brain. Recovery uneventful and discharged in nine days.

*Recent Behavior.*—Patient is timid, afraid of the dark, bites his nails, and has nocturnal and diurnal enuresis. He only plays with younger children. He cannot stand being scolded. He always learned slowly and forgot easily. Repeated first grade and is repeating second grade.

*Home Environment.*—The father is a bus driver who didn't go far in school. The mother divorced him because he wouldn't support her. She remarried a man by whom she had two children. Mother thinks patient is like his father. She is an immature, nervous person who scolds and nags patient, but is fearful about his health.

*Examinations.*—Physical and neurologic examinations were negative except for an injected pharynx.

*Psychologic.*—Stanford-Binet: chronologic age, nine years seven months;

mental age, eight years four months; I. Q., 86. Tests ranged from seven to ten years. Rating: dull normal intelligence.

*Psychiatric.*—Patient said mother left father as he got drunk and used to beat mother. Patient sees father but if he comes near the house mother has him arrested. Mother worries a lot about his health and restricts his play for fear he'll get in trouble. His stepfather beats him a lot. Both parents favor his baby sister. Patient tells of the accident and adds that two years later a boy threw a stone and hit his head on the spot that was injured previously.

*Interpretation.*—Patient is immature in his emotional development and feels insecure. He has conflicts about his parents' separation and he is uncertain regarding his mother's love. His enuresis is partly due to this insecurity. Some of his present symptoms are due to his mother's anxiety regarding him and her exaggeration of the importance of the accident.

*Treatment.*—Patient and mother were asked to return to the clinic but did not return in the past three years.

**Case VII.—Reason for Referral.**—W. S., a thirteen-year-old white boy, in the seventh grade, was referred in November, 1933, to the clinic, thirteen months after his accident. He has been nervous and had headaches ever since his accident.

*Development.*—Second of 3 children. Birth and development normal. Was a happy, ordinary child until his accident. Repeated the fifth grade. Tonsils removed at three years. Has worn glasses since six years old.

*Accident.*—At twelve years of age patient was hit by an auto and received laceration of the shoulder and injury to his head. No skull fracture, or unconsciousness.

*Recent Behavior.*—Mother claims he has been nervous ever since his accident. He gets severe headaches and has periods of feeling weak and dizzy. These come on after reading, or after some unpleasant incident, as being scolded. Is upset by the least thing. Gets irritated at his mother, saying "Don't worry me. Leave me alone." Is afraid his father will harm him bodily.

*Home Environment.*—The mother divorced the patient's father when patient was four years old. She remarried. Three years ago mother had a "nervous breakdown." She seems very unstable. She fears the father will take patient away or harm him, so she frequently warns patient to avoid the father.

*Examinations*—Physical and neurologic examinations were essentially negative.

*Psychologic*—Stanford-Binet: chronologic age, thirteen years four months; mental age, fourteen years three months; I. Q., 107. Tests ranged from twelve to eighteen years.

*Rating.*—High average intelligence.

*Psychiatric*—Patient seems like a weakling and very dependent on his mother. Says he hates his father as he was mean to mother. Both he and mother are nervous. She is always after him not to play rough or he'll get hurt. He is especially jealous of his half-brother. Describes quarrels and disagreements regarding discipline between his parents.



*Interpretation.*—Patient's nervousness is largely a reaction to his mother's neurotic behavior and her anxiety that he was seriously injured in the accident. Patient sides with mother in his thinking and he also feels the accident made him nervous. He also sides with mother against the father and shows a little resentment at mother for remarrying and having more children. Patient is developing neurotic tendencies.

*Treatment.*—Psychiatric treatment at the clinic was offered but neither patient nor his mother has returned in three years.

**Case VIII.**—*Reason for Referral.*—N. K., a ten-year-old white boy, in low fifth grade, was referred in September, 1936, to the clinic, seven years after his accident. He has stuttered ever since his head injury.

*Development.*—Third of 4 children. Birth normal, breast-fed nine months. Development normal. No serious illnesses, food fads or nervous habits. Has a good disposition and is popular with children. In school repeated high fourth grade. Is slow in his work.

*Accident.*—When three and one-half years of age patient was hit on the head by a golf club. His head was severely cut and several stitches were necessary. Patient's stuttering started immediately after this. The physician who attended him said it was due to the fright and shock and that he would outgrow it.

*Recent Behavior.*—Patient has stuttered ever since his head injury. He does it most when he is excited. He is very much ashamed of this handicap, especially as it interferes with school recitations. He is afraid of doctors and hospitals. On the whole he has a pleasant personality and gets on well with children and adults.

*Home Environment.*—The father is well educated and kindly but not able to support the family very well. The mother married at sixteen years and feels she has missed the good times her friends have had. She is a little rebellious at her husband's old-fashioned ideas, and her lack of recreational opportunities. She is quite worried about patient. Both parents put quite a bit of educational pressure on their children.

*Examinations.—Psychologic.*—At nine years ten months of age patient was given the National Intelligence (group) Test and received an I. Q. of 105.

Stanford-Binet: chronologic age, ten years eight months; mental age, nine years; I. Q., 84. Tests ranged from eight to ten years.

*Rating.*—Dull intelligence.

On a series of 10 performance (manual) tests patient obtained an average mental age of nine years. Patient is right-handed.

*Retest* after seven months of treatment.

Stanford-Binet: chronologic age, eleven years three months; mental age, ten years one month; I. Q., 89. Tests ranged from eight to twelve years.

*Rating.*—Dull normal intelligence.

On a series of 12 performance tests patient obtained an average mental age of ten years.

*Psychiatric.*—Patient describes his father as being very punishing, especially if patient gets poor marks in school. Patient's ambitions, to be a doctor or lawyer, are definitely beyond his ability. Patient shows extreme jealousy of

his fifteen-year-old brother. They fight every day. "I half kill him." In the interview patient stuttered only when the topic upset him.

*Interpretation.*—Patient's stuttering seems to be a neurotic trait, started by the mother's marked anxiety at the time of his accident. It continued as a habit because by it he derives the infantile satisfaction of having his mother continue to show anxiety and be protective of him.

*Treatment.*—He was seen for 7 psychiatric interviews and has had weekly tutoring and remedial exercises by the psychologist for a period of seven months. Patient has shown definite and steady improvement.

*Case IX.—Reason for Referral.*—W. B., an eleven-year-old white boy, in low fifth grade, was referred in January, 1936, to the clinic, five years after his accident. He fights a lot, bites his nails, sucks his thumb, masturbates, wets his bed, walks in his sleep and daydreams a lot.

*Development.*—Second of 5 children. Birth and development were normal. Was bottle-fed until eighteen months of age. Usual childhood diseases. At three years of age was severely ill with pneumonia. Has had growing pains and joint pains, claims he doesn't hear well.

*Accident.*—When six years old patient was hit by an auto. He was unconscious and came to in the hospital. x-Ray showed a linear fracture in left parietal region. No depression. Recovery uneventful and patient was discharged after nine days.

*Recent Behavior.*—Patient is irritable, fighting frequently with his younger brother. If scolded or whipped he becomes sullen. He tends to be seclusive. He is repeating his grade in school for the first time. See above for list of his problems. He has always had nocturnal enuresis.

*Home Environment.*—The father was brought up strictly. He is a dull, ignorant man who drinks a lot, quarrels with his wife, neglects his children and shows serious neurotic symptoms. The mother was brought up in an extremely unstable home (her mother being psychotic). At fifteen years of age she was sent to a girl's reformatory for one year. She has been very promiscuous ever since she was sixteen years old. She spends only a few hours a week at home. She is a notorious drunkard and fighter. She was sentenced to a year in jail. The home was broken up and the children placed in foster homes.

*Examinations.—Physical.*—Patient is undernourished. Tonsils moderately enlarged and infected. Anterior cervical nodes large and tender. Slight tenderness of knee and elbow joints. Dental caries. Gait is springy, favoring left side. Carries left arm semiflexed. Reflexes active but equal. No pathologic reflexes. Tonsillectomy and dental care were recommended.

*Psychologic*—When patient was ten years old he was given the Illinois Intelligence (group) Test and was given an I. Q. of 116.

Stanford-Binet chronologic age, eleven years one month; mental age, ten years ten months, I. Q., 98. Tests ranged from ten to fourteen years.

*Rating.*—Average intelligence

On a series of 9 performance (manual) tests his average mental age was nine and one-half years. Goodenough drawing test: score, 49

This is equivalent to a mental age of nearly fifteen years. His drawing shows some talent.

*Psychiatric.*—Patient describes his mother's neglect but tries to defend her. He describes his father as being very strict and punishing severely. He feels insecure and unhappy. He was in uncle's home a while and hated it. He dislikes his present boarding home. He shows rather strong ties to his family. On the whole he has a repressed, colorless personality.

*Interpretation.*—Patient's head injury has little to do with his present behavior. This is largely affected by his extremely unstable home setting.

*Treatment.*—It was recommended that he be placed in another foster home. This was done and in ten months practically all of his symptoms have disappeared, including his enuresis.

**Case X.—Reason for Referral.**—H. B., a seventeen-year-old white boy, was referred in June, 1935, to the clinic, seven years after his accident. He has run away from home several times.

*Development.*—Second of 3 children. Was one and one-half years old when his mother died and was raised by his paternal grandmother. Birth, health and development were normal except for some retardation.

*Accident.*—At ten years of age patient was struck by an auto. He was unconscious for two days and was in the hospital four months. (The hospital never replied to our letter asking for a report.) Since then patient has been hit on the head twice and was unconscious both times.

*Recent Behavior.*—Since his accident patient became disobedient in school and was taken to Juvenile Court because of truancy. He also began running away from home and did this frequently. Grandmother blames this on the head injury. Patient quit school at sixteen years in the seventh grade.

*Home Environment.*—Mother died (soon after the birth of her third child) when patient was one and one-half years old. Was raised by his paternal grandmother who was very strict and punished patient a lot. Patient was his father's favorite and was treated very leniently by him. Father and grandmother frequently quarreled regarding patient's discipline.

*Examinations.—Psychologic.*—Stanford-Binet: chronologic age, seventeen years; mental age, eleven years six months; I. Q., 72. Range nine to sixteen years.

*Rating.*—Very dull intelligence.

A series of 12 performance (manual) tests gave him an average mental age of fourteen years.

*Psychiatric.*—Patient describes himself as being spoiled by his father. He describes his grandmother as being very strict, but since his accident she has feared he will be a criminal. Patient has many feelings of inferiority which were intensified by his accident. Thus his younger brother passed him in school since the accident. Also since his accident he became afraid of playing baseball. He began going with a tough gang of boys, trying hard to win their approval.

He seems somewhat unstable and will lose jobs but the general prognosis seems fair in the sense that he will be able most of the time to support himself and will not be markedly antisocial.

*Treatment.*—It was recommended that he be treated by the traveling psychiatric clinic that visits his home town. If adjustment fails he might either be sent to a C. C. C. camp or the State Industrial School for a period.

*Case XI.—Reason for Referral.*—L. B., a twelve-year-old colored boy, in third grade, was referred in March, 1936, to the clinic, six years after his accident. He runs away from home, steals and has "spells."

*Development.*—Third of 7 children. Birth and development normal. Tonsillectomy and adenectomy at eight years of age.

*Accident.*—At seven years patient was hit by a street car and dragged some distance, receiving scalp lacerations. The mother collected \$150 plus medical care as compensation. (The hospital never replied to our letter asking for a report.)

*Recent Behavior.*—A year after the accident patient started running away from home and did so almost continuously to the present. He has been picked up by the police and brought to Juvenile Court innumerable times. Occasionally he steals. He usually travels alone and tells people how badly treated he is at home. He was sent by the court to three different institutions. He was sent twice to the State Industrial School for Colored Boys but ran away so often they refused to accept him again. His school attendance has been extremely irregular. He recently complains of headaches and spitting up of blood. His mother says that in the past month he has had two "spells" of fainting. The mother blames all of patient's trouble on the accident.

*Home Environment.*—The mother has had 7 children by 3 men. Only 1 of her children is legitimate. The patient is illegitimate. The mother never lived with the father although she bore him 4 children. The mother does domestic work and is away all day and has no control over her children. Of her children the patient is the most uncontrollable. She has had treatment for syphilis.

*Examinations.—Physical.*—Scalp scar over left frontal and temporal region. Mucous membranes pale. Small, shotty glands palpable in the neck. Chest examination negative. Right pupil larger than the left. Both react normally.

x-Ray of chest is negative.

Blood Kolmer test is negative.

*Psychologic.*—Stanford-Binet: chronologic age, twelve years nine months; mental age, seven years two months; I. Q., 56. Tests ranged from six to nine years.

*Rating.*—Feeble-minded.

*Psychiatric.*—Patient was extremely resistive. Sat staring at the floor with expressionless face and answered all questions in monosyllables. His usual answer to everything was "Nothin'."

*Treatment.*—It was recommended that he be placed in the State Industrial School for Colored Boys until he could be transferred to the new school for colored feeble-minded which had not yet been opened.

*Case XII.—Reason for Referral.*—A. I., a ten-year-old white boy, in low fourth grade, was referred in January, 1933, to the Cleveland Clinic, fourteen

months after his accident. Ever since his accident he has had violent temper outbursts, fighting and throwing anything he can reach.

*Development.*—Sixth of 9 children. Mother was very ill in pregnancy, having two severe hemorrhages. Mother nearly died at birth, which was cesarean. She had to have a transfusion. Patient was bottle-fed as mother had no milk. Patient had diphtheria at sixteen months of age. Development was normal, and patient was healthy until his accident.

*Accident.*—When nine years old patient was hit by an auto and received scalp lacerations. His left leg was broken at the hip. His hip was operated on four times, and he was in a cast, then on crutches and finally a brace. The mother is very emotional about the accident. She wants the clinic to help her collect damages and says she is sure patient's mind was affected.

*Recent Behavior.*—Patient's personality changed since the accident. He has violent, explosive temper outbursts in which he fights his brothers. Mother fears he will hurt someone. He has had none of these outbursts at school. At home he also shows marked food fads. Says, "I won't eat even if you kill me."

*Home Environment.*—The father is illiterate. He is very irritable and frequently fights with mother. He is being treated for syphilis. He has been in 3 accidents and tried unsuccessfully to sue each time. The mother is twelve years younger than father. She has been so unhappy in her marriage she is very resentful toward her mother who arranged it. She is very emotional especially when talking about patient's accident and behavior.

*Examinations.—Physical.*—Undernourished. The rest of the examination was essentially negative. Tuberculin test negative.

*Psychologic.*—Three years before the accident patient was given the Stanford-Binet: chronologic age, six years; mental age, five years ten months; I. Q., 97.

Fourteen months after the accident he was given the Stanford-Binet: chronologic age, ten years; mental age, nine years eight months; I. Q., 97.

*Rating.*—Average intelligence.

*Psychiatric.*—The patient describes his mother as losing her temper with patient but also as worrying too much about him. He admits liking this in some ways but still feels it is too much. His accident looms large in that he speaks of it several times spontaneously. Some of his attitudes and behavior are quite infantile. Fortunately he is very fond of his teacher and likes school.

*Treatment* was directed more at trying to lessen the mother's anxiety and emotional tension regarding patient. This was carried on two months (when the clinic closed) and was moderately successful.

*Case XIII.—Reason for Referral.*—C. S., an eight-year-old white boy, in low second grade, was referred September, 1934, to the clinic, five months after his accident. He is nervous, has headaches and is failing in school.

*Development.*—Third of 4 children. Birth and development were normal. Breast-fed ten days. Was on a bottle for two years. At three years he had scarlet fever and the family physician said he would have "weak kidneys." At five years of age patient was in an auto accident in which he was not

injured but a girl sitting beside him was decapitated. Patient was very nervous for several weeks, trembling and showing choreiform movements.

*Accident.*—See above for accident at five years.

At seven years of age patient was knocked down by a taxi and the right clavicle was fractured. No unconsciousness or evidence of head injury. Father collected damages out of court. Immediately after this accident patient became nervous, trembling and choreic, as with the previous accident.

*Recent Behavior.*—Ever since his first accident he has shown frequent and severe displays of temper, screams, throws things and has attacked his parents and his younger brother with a knife. He only plays with younger children and he is cruel to them. At school he is very troublesome, is punished a great deal and is failing. He is afraid to go to bed without a light. He has a poor appetite. He has frequent nosebleeds and headaches. He is extremely restless and hyperactive. His mother blames all these symptoms on the accident. She is sure his brain was injured and that he is losing his mind.

*Home Environment.*—The father has been ill with diabetes and tuberculosis and has been a poor provider. He drinks, stays out late at night and is mean and ugly to his wife. He shows no interest in the children and is especially irritated by patient. He calls patient unprintable names, hates to see him around and frequently threatens to have him "put away." The mother was sixteen years old when she was married and has been sorry ever since, he is so mean. She shows mixed feelings and behavior toward patient. She has been too lenient, giving in when he has a tantrum and being protective when father is mean to him. On the other hand patient gets on her nerves so that she can't stand him any longer. She becomes very sarcastic about him, scolds a lot and insists that he has to be placed somewhere. She fears patient will be like his father, get tuberculosis or lose his mind. The family lived with the maternal grandmother who also protected patient. He would run to her whenever his parents punished him.

*Examinations.*—*Physical.*—Patient has had many careful physical and neurologic examinations and no basis has been discovered for his headaches and nosebleeds. Tonsils were enlarged and were removed, eyes were examined carefully and findings were negative. At mother's insistence he was examined in the tuberculosis clinic and findings including tuberculin were negative.

*Psychologic.*—Stanford-Binet: chronologic age, eight years four months; I. Q., 84. Tests ranged from six to eight years.

*Rating.*—Dull normal intelligence.

Rogers Test of Personality Adjustment showed a high degree of maladjustment in every category but "daydreaming" which was low. The "social" and "family" maladjustments were especially marked.

Furfey Test for Emotional Development gave a Development Quotient of 88.

*Psychiatric*—Patient describes his mother as being overly anxious about his health and school work, "She doesn't want me to get killed. She wants me to take all the schools." He describes his father as being severe and openly rejecting. "He doesn't care about us. He says he's going to put us away." Patient is most upset by his mother's mixed behavior. He shows a definite

anxiety reaction regarding his accidents, and this has been intensified by his mother's concern.

*Treatment.*—Patient was placed in a children's convalescent school for five months. During this period he showed marked improvement physically and mentally. This improvement only lasted a few weeks after his return home. Treatment at the clinic was attempted, but the mother did not cooperate, insisting she only wanted placement. Patient was referred to a child-placing agency for placement in a foster home.

*Case XIV.—Reason for Referral.*—H. C., a nine-year-old white boy, in opportunity class, was referred in March, 1935, to the clinic, three years after his accident. He seems unable to learn to read.

*Development.*—Youngest of 3 children. Mother was very ill during the pregnancy. While mother was pregnant patient's four-year-old brother was kicked in the head by a mule and was unconscious some time. Mother then felt no "life" and thought patient had died. Birth was difficult as the baby was large. Breast-fed only two months as mother's milk was poor in quality. When cutting teeth he had convulsions. At two and one-half years he had a mild case of chickenpox followed by pneumonia, at which time he was delirious during the fever. At six years he cut his toe on a bicycle and it had to be amputated. After returning from the hospital he had occasional nocturnal and diurnal enuresis.

*Accident.*—At six years of age (six months after returning from the hospital) patient fell off a truck, cut his head and became unconscious. A private physician sewed him up and sent him home. He soon vomited and became unconscious again. He was taken to a hospital and diagnosed cerebral concussion. Two x-rays were negative for fracture of skull. Physical examination at the time was negative except for lacerations of the scalp, supra-orbitally, and semiunconsciousness. Spinal fluid was not examined. Recovery uneventful and discharged in six days.

*Recent Behavior.*—Patient shows hardly any signs of nervousness. He is pleasant, obedient and gets along well with other children. His main difficulty is his inability to learn to read. The father blames this difficulty on patient's head injury. Patient is very sensitive about his disability as children taunt him about it. Teachers say he is dull and when eight years old he was placed in the opportunity class.

*Home Environment.*—The father is a very nervous, high-strung, quick-tempered man who had a nervous breakdown (when patient was born and his brother was injured in the head) and he was incapacitated for four years. He frequently attempted suicide. The mother had an unhappy life as a child (broken home) and seems overwhelmed by her present home. She has been ill and weak since the birth of her first child and her husband has been incapable of supporting the family since his breakdown.

*Examinations.—Psychologic.*—At six years Detroit Group Test, I. Q., 96. Stanford-Binet: chronologic age, seven years four months; mental age, six years two months; I. Q., 84. Tests ranged from four to eight years. Stanford-Binet: chronologic age, nine years two months; mental age, eight years four months; I. Q., 91. Tests ranged from five to ten years.

At nine and one-half years, Metropolitan Reading Test, 1.7 grade.

At nine and one-half years, Metropolitan Arithmetic Test, 2.3 grade.

Dull normal intelligence rating.

Average ability on a series of performance tests.

On a series of tests for specific reading disability (Gates and Betts) he showed some tendency to reversal of letters, very poor phonetic ability and visual memory. His vision and acuity of hearing were normal and there was no eye muscle imbalance.

*Psychiatric.*—Patient showed a slight speech defect resembling a stutter. He is showing a few neurotic tendencies. He describes his mother as being markedly overanxious about his health and about his reading. He is somewhat afraid of his father. Both parents say he must be "dumb."

*Treatment.*—Patient was referred to a teacher who specialized in tutoring children with reading disability. The last report indicated that he had made marked improvement in his reading and was much happier.

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### ACUTE EMPYEMA IN CHILDREN: DURATION OF ILLNESS PRIOR TO TREATMENT A FACTOR IN MORTALITY RATE

THE modern conception of the basic principles in the management of pleural empyema was established by the report of the Empyema Commission<sup>1</sup> of the United States Army in 1918. This work has stimulated considerable interest during the past twenty years in the creation of better methods of treatment. The concentration of thought in many instances has been centered upon various methods of technic which are a revival of the principles of suction, siphonage or valvular action.

Many authors have claimed that their results are primarily or entirely due to some particular method of operation. A close scrutiny of the many statistical reports bare conflicting evidence and leave one in a quandary as to which is the best operative procedure. It is to be admitted that variable percentages in the reports of death rates may be influenced by the type and virulence of the infection, or by monthly and seasonal variations. These factors will affect mortality rates regardless of the type of treatment.

The object of this report is to stress with particular emphasis a point which has heretofore received little mention. The particular point for discussion is: *the duration of illness prior to treatment as a factor in empyema complications as well as a factor to be considered in the deduction of mortality rates irrespective of the type of operative procedure.* The

duration of illness has considerable bearing on the development of complications, from which, in most instances, death must be attributed. Patients rarely die from empyema per se. Death may be due to septicemia, meningitis, brain abscess, pericarditis, lung abscess, liver abscess or peritonitis. One frequent complication not to be overlooked is postoperative pneumonia in the contralateral lung.

Our information is based on a study of 103 cases of acute empyema in children under thirteen years of age who were

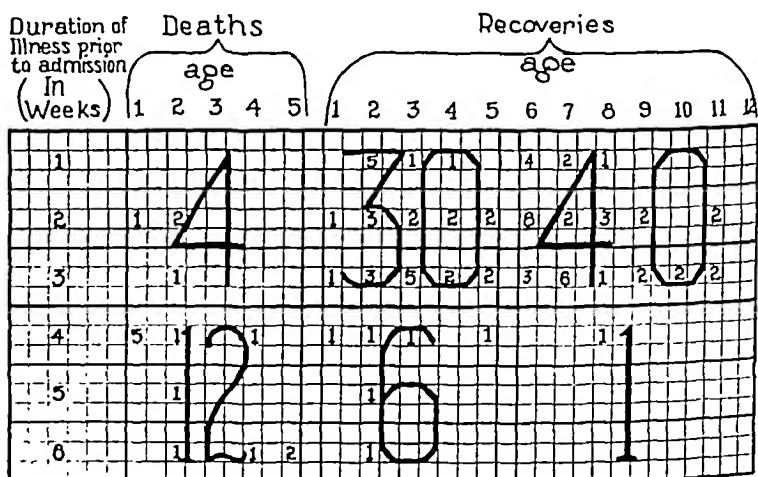


Fig. 95.—This chart represents a study of the duration of illness, in weeks, prior to admission. The death and recovery cases are bracketed in separate columns. The smaller figures indicate the number of cases for the particular ages while the larger figures represent the total numbers in each square. Note the heavy line of demarcation between the third and fourth weeks in duration of illness. Twelve deaths occurred in the younger children who were ill more than three weeks prior to admission and treatment.

treated at the University Hospital from 1924 to 1934. The usual statistical findings in this group parallel those of similar reports found in the general hospital series.

The duration of illness prior to treatment was determined conclusively in 93 of the 103 cases. Twelve of the 16 deaths occurred in patients who had been ill more than three weeks. In the group of recoveries, 70 cases were ill three weeks or less, while 7 cases had been ill more than three weeks prior to receiving treatment. A sharp line of demarcation between the

fatal and the recovering cases fell between three and four weeks from the onset of the initial illness (Fig. 95).

It is a striking fact that no death occurred in the 44 children who were between six and twelve years of age (Fig. 96). The cause of death in 14 cases was proved by necropsy to be one or more of the complications mentioned above. Why did these deaths occur? With this point in mind the question was studied with respect to the type of infection and the duration of illness. Most of the deaths occurred irrespective of the type of infection in those cases who had been ill

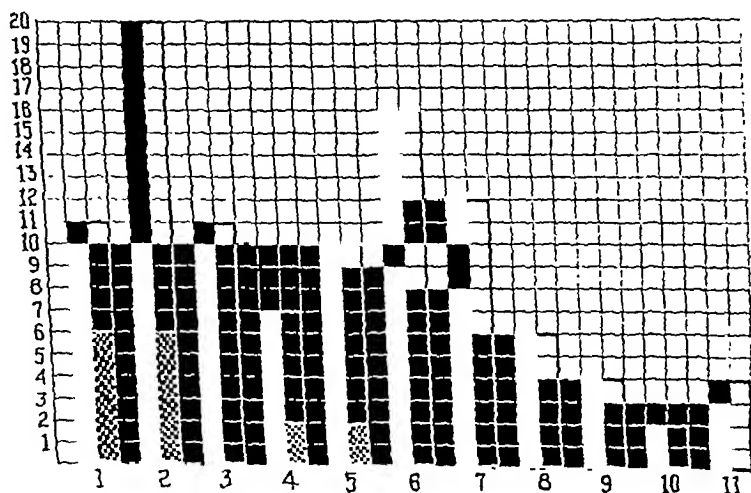


Fig. 96.—The solid black columns represent the total number of cases of empyema for each year of age. The hatched columns indicate the number of deaths at the various ages. It is to be noted that there were no deaths between the ages of six and twelve years.

more than three weeks and many recoveries were found in the group who had been ill three weeks or less (Fig. 97).

It is reasonable to suspect that the delay in receiving treatment is due to the late diagnosis of pneumonia and empyema in the very young children. Complications are more apt to follow as a result of this delay. Therefore, higher mortality rates are to be expected. The treatment in some of this series of cases consisted of aspiration alone; in others, aspiration combined with open and closed methods of drainage with and without rib resection was done. The results are not attribut-

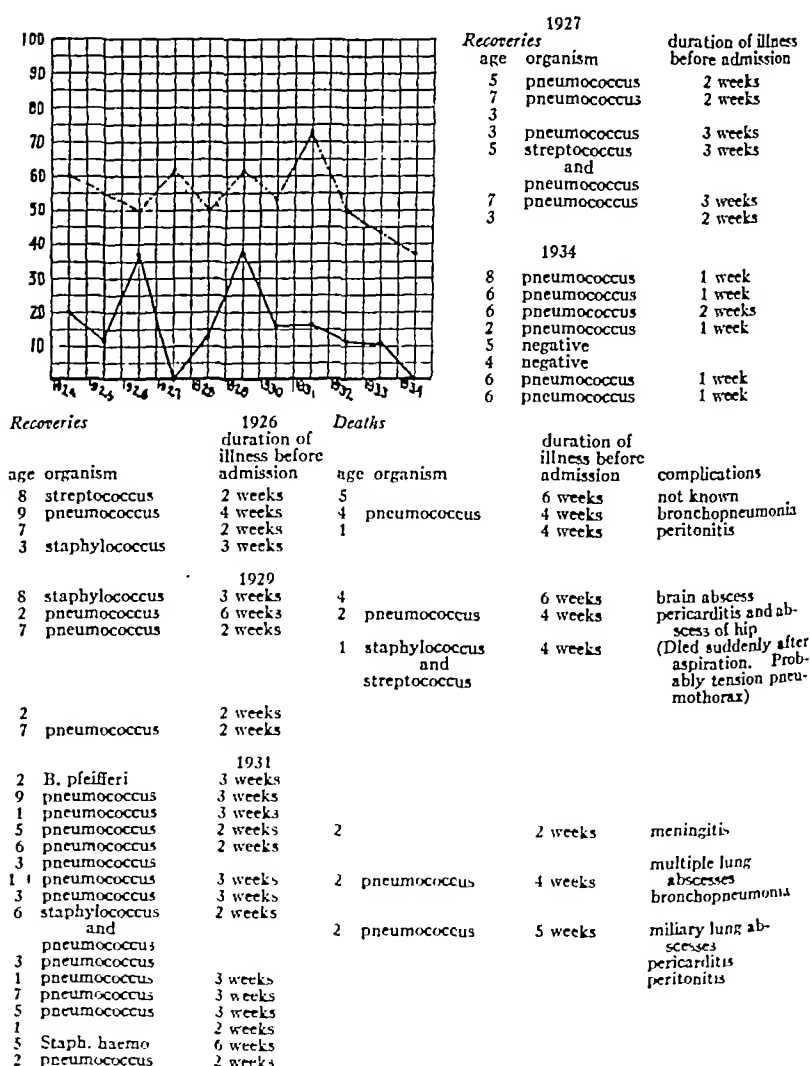


Fig. 97.—The solid curve in the graph shows the mortality rate per year in the 103 cases of empyema. The dotted curve represents the percentage of cases (five years of age or less) for each year. It is to be noted that the variable mortality rates for different years are not due entirely to the fact that most cases were in the very young age group. The high percentage of younger children in 1931 shows a comparatively low mortality rate. The mortality rates for 1926 and 1929 are tabulated with the ages, recoveries, duration of illness and type of infection. The duration of illness is an important contributing factor in these years of higher death rates. There are no deaths in 1927 and 1934. Note the duration of illness before admission, in the tabulated cases for these two years.

able to any one particular method of treatment. In these 103 cases there was not a single fatality among the group that developed empyema while being treated in the hospital.

### CONCLUSIONS

Any child suffering from suspected pneumonia, particularly those under six years of age, who show little or no improvement after ten days from the onset of illness, should have an x-ray examination of the chest. It is an ordinary precaution. Early recognition with proper treatment will greatly reduce the mortality in empyema.

It is not to be construed that the plea for early diagnosis is also an appeal for immediate operation after the diagnosis has been made. The individual factors in each individual case, such as the type and virulence of infection, the general condition of the patient, the consistency of the pus and the location and character of the empyema, should be some of the determining factors in selecting the time and plan of treatment.

The duration of illness prior to treatment may be a helpful index in the prognostication of complications and mortality rates.

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### DIAGNOSIS OF THE CAUSES OF LOW-GRADE ABDOMINAL PAIN IN CHILDREN

VAGUE recurring abdominal pain is a common complaint in children. It is a complaint that most frequently is uttered in the age group of three to ten years.

The pain presents no definite characteristics, with the exception of its almost constant localization to the umbilicus.

The causes of the condition are manifold, ranging from local disturbances to those far remote from the abdomen. The nature of the disturbances may be serious or comparatively trivial. Because of the numerous etiologic factors involved, and their associated variable nature, it behooves the physician to definitely arrive at a diagnosis.

To reach a diagnosis is frequently a complex problem as the complete absence of any pathognomonic subjective or objective findings is notable in this complaint. Therefore, confronted with the condition the only premise that can be advocated is—be thorough!

The citation of cases, exemplifying confirmation of the above statement, is probably the most satisfactory manner of illustrating diagnostic procedures.

Case I.—A colored boy, aged four years, was admitted to the University of Maryland Hospital with the complaint of vague, recurrent umbilical pain of several months' duration. Vomiting had been present for the past two days. The patient had had a similar attack one month prior to admission; at which time a diagnosis of "acidosis" was made.

The diagnosis of the condition in this youngster would have remained obscure, but for our routine inquiry as to the history of paint eating. Such a history was obtained and

substantiated by the presence of a lead line in roentgen-ray examination of the long bones. While lead poisoning is more common in infants, it is seen in older children. We strongly feel, however, that the diagnosis will seldom be made short of the encephalitic stage, unless routine inquiry is made in history taking. Peripheral neuritis, lead line and other adult features are usually absent in children. Yet the diagnosis can easily be confirmed or excluded by demonstration of the typical lead line in the long bones. This case is an excellent example of the importance of thorough history taking.

**Case II.**—A white boy, aged six years, was seen complaining of umbilical pain at recurring intervals for the past six months. There had been a concomitant anorexia, slight loss of weight and some lassitude. The history was strongly suggestive of tuberculosis: yet contact was denied. On examination definite nodular masses could be palpated in the region of the cecum. The Mantoux test in a dilution of 1:1000 was strongly positive. A flat plate of the abdomen revealed the presence of calcified glands.

The mesenteric glands are frequently the site of tuberculous infection. As a rule they give rise to very vague and unreliable symptoms and physical signs. When pain is present it is chiefly attributable to acute glandular inflammation, periaadenitic edema and local peritonitis of the adjacent serosa. The location is usually umbilical or lower right quadrant. The routine use of tuberculin testing, as a diagnostic aid in conditions of vague abdominal pain, is unreservedly urged, for the tuberculin reaction is of great significance when negative in that it provides very dependable evidence against the presence of tuberculosis. The diagnostic usefulness of roentgenography is almost exclusively limited to the demonstration of the old calcified stage of the disease.

**Case III.**—A white boy, aged ten years, was seen with the complaint of umbilical pain, usually following the ingestion of food. The complaint had been present since the age of three years. The pain was described as cramp-like and frequently associated with vomiting. The past history elicited the information that the child had vomited frequently as an infant and was termed a "feeding problem." As to the family, the patient was the lone child of parents who were lone children of their respective families. When examined the child presented a picture of combined malnutrition and nervous fatigue. Naturally there was a very strong tendency to class this patient as a behavior problem. But, because of the long duration of the complaint, he was subjected to a complete clinical investigation. A gastro-intestinal x-ray revealed

a definitely delayed emptying time of the stomach, which apparently was due to some obstruction below the duodenum. Operation was advised and peritoneal bands of adhesions were released.

The frequency of similar conditions is undoubtedly difficult to determine, as children suffering from peritoneal bands causing chronic manifestations present so many signs of nervousness that they are almost invariably classed as "the behavior child." Their pain varies from a feeling of heaviness to attacks of severe colic. Vomiting is outstanding, usually coming on after eating. In some cases the vomitus may contain food which has been ingested some hours before.

Case IV.—A white girl, aged nine years, was admitted to the hospital with the complaint of recurring umbilical pain for the past four years. There were associated symptoms of anorexia, failure to gain weight, fatigue, occasional nausea and car sickness. In the family history it was noted that the patient was the younger of 2 children and that there was a difference of eight years in their ages. On examination, the patient was of the asthenic type: the color was sallow; a marked lordosis was present, the scapulae were winged and the abdomen was prominent. A combination of findings which constitute a picture of nervous fatigue—a very extensive investigation was productive of entirely negative results.

This patient falls into an untermed group. Members of this group are felt by Cameron to manifest a definite ketonemia, though confirmation of this hypothesis is lacking. The abdominal pain is probably due to ptosis. However, these children when placed on a high carbohydrate, low fat diet plus adequate rest and systematic exercise for the correction of the postural defects and the hypotonia do surprisingly well. The diagnosis at the present time can only be made by exclusion.

Case V.—A white girl, aged seven years, was seen complaining of pain in the lower right quadrant, occurring at varying intervals during the past two years. The attacks were usually associated with some vomiting. Seen at the time of the attacks nothing of significance could be determined. The family history was of especial interest. The mother had been classed definitely neurotic, because for the past three years she would arise in the morning and have a bout of vomiting, complaining of severe abdominal pain. About six months after the onset of the mother's dilemma, the patient's brother, aged fifteen years, began to have the same symptoms. All of the family had been accorded a very complete investigation by their physician, with negative results.

It was felt that this patient should be accorded a laparotomy. The reason being that the appendix might be the offender because of the localization, the

vomiting and persistence. Neuroticism was strongly suggested and considered the most probable cause. Yet, at operation an appendix which had been the seat of repeated infections was removed.

Chronic appendicitis is the condition immediately suspected whenever abdominal pain is present. The diagnosis rests entirely on seeing the patient in an attack. Rectal examination gives a great deal of information in these patients and should never be neglected. The value of roentgenograms is subject to some difference of opinion, but they often give quite valuable information.

**Case VI.**—A white boy, aged eleven years, was seen with the complaint of recurrent attacks of abdominal pain. The pain was described as appearing in the lower right quadrant. There was nothing further of interest in the personal history. The family physician volunteered the information that during the attacks there was elicitable tenderness over the lower right quadrant, with no spasticity or rigidity, and rectal examinations had been negative. The family history gave a definite statement as to the presence of hives and asthma in various other members. Following this lead it was elicited that the boy intensely disliked eggs, but the parents did not think that the condition showed any tendency to be related to the intake of this particular food.

It was felt that with the strong allergic history in the family that the abdominal symptoms might be on an allergic basis, so it was suggested that eggs be fed the patient and the reaction, if any, noted. The advice was followed and the ingestion of eggs on the first occasion provoked a bout of abdominal pain. Their use on a second occasion was followed both by pain and an urticarial rash.

The history of allergy in the family should always make one suspicious that the abdominal pain symptom-complex might be due to hypersensitiveness. Certain food dislikes should not be overlooked, for these when forced may produce abdominal pain with definite allergic manifestation. Eosinophilia is very helpful and is probably present in a great number of these cases. The leukopenic index may be of assistance, but we unfortunately have had no experience with it. Cutaneous tests have not been helpful. The opinion has been expressed to explain this latter feature, that in gastro-intestinal allergic conditions the clinical reactions of the allergens are of the cumulative type.

#### DISCUSSION

A small group of patients illustrating a few of the causes of low-grade abdominal pain, and the diagnostic procedures

utilized in arriving at the cause have been presented. Obviously the list is not complete, as the literature contains numerous articles on this subject.

The difficulty of making a diagnosis in these conditions is readily seen. Thoroughness is the only reliable agent that the physician possesses.

In reaching a diagnosis a complete and exhaustive history and physical examination are essential. In taking the history the daily habits of the child, his diet, and his emotional life need investigation. The importance of psychic factors in the production of abdominal pain should however be taken with a grain of salt. Careful inquiry as to any history of allergy in the family should be made. Food idiosyncracies should receive their full attention.

The physical examination should be very thorough. That sinusitis and allied respiratory infections may be responsible for the complaint, through their production of adenitis, should be remembered. Rectal examination, as a routine procedure, should not be forgotten. It has been said that the difference between the practitioner and the surgical consultant is that the surgeon makes a rectal examination. More attention should be given to the importance of blood pressure determinations in children, as elevations may lead to the detection of heavy metal poisoning, adrenal tumors, kidney tumors, etc., conditions which while rare may have as the initial complaint abdominal pain. We recently saw a case of an adrenal neuroblastoma in a boy of six years, with a blood pressure of 160/130, who has been complaining of abdominal pain for six months.

Examination of the blood, urine, and stool, should be carried out as part of the initial visit. Some of the vague blood dyscrasias may play a rôle in the causation of abdominal pain. Repeated leukocyte counts and sedimentation tests may be of assistance in diagnosing those conditions due to a rheumatic infection. The importance of urinary tract infections as a factor in the production of abdominal pain is fairly well stressed. However, their diagnosis will not be made unless the urine is examined. That dark-colored stools due to the presence of occult blood are probably the most constant finding in duodenal and gastric ulcers is important. Intestinal para-

sites are probably not so common a factor as thought, but must necessarily be considered.

Tuberculin testing is an easy procedure to carry out and should be made routine in examination.

Constipation is frequently responsible for abdominal pain and when present, corrective methods should be advised. Intestinal spasm, either as an accompaniment of constipation, or as a separate entity, can be excluded by the failure of the symptoms to respond to belladonna and a low residue diet.

After the cases have been thoroughly and systematically studied as above outlined, and with no definite cause being found, and with a failure of the symptoms to respond to a regulation of diet and life, investigation of the gastro-intestinal tract by roentgenography is indicated. Pyelographic studies should be advised where renal calculi and anomalous conditions of the urinary tract might be suspected. Biliary calculi are comparatively rare, but when a possible factor gallbladder visualization might be of assistance.

The great majority of causes of low-grade abdominal pain in children are undoubtedly comparatively trivial. This fact has given rise to the unfortunate tendency on the part of the physician to adopt the line of least resistance and classify all cases as due to one or the other of these trivial factors. As a consequence when confronted with a problem that fails to fit into his limited category, he is very much at a loss. This is a most unfortunate situation, as one will make less mistakes and more correct diagnoses if the policy of exhaustive thoroughness is adopted.

## CLINIC OF DR. T. CAMPBELL GOODWIN

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### THE TREATMENT OF ACUTE NEPHRITIS AND ITS COMPLICATIONS IN CHILDHOOD

SINCE there are so many classifications of nephritis in childhood it is well to define the term "acute nephritis" as used in the title. We speak of that condition which usually, if not always, follows an acute infection and is termed by various writers "acute glomerular nephritis," "acute hemorrhagic nephritis," "acute postinfectious nephritis," "acute focal nephritis" and "acute diffuse nephritis." The symptoms and course of this general systemic disease are too well known to warrant discussion here, but for purposes of clearness it is well to give the characteristics which serve to distinguish it from other types of nephritis. The sudden onset follows a few days or a few weeks after an acute infection but the symptoms may begin while the infection is still present. Edema, seldom extreme, is nearly always recognizable, and hypertension is the rule, although it may not be severe. The urine is reduced in amount and contains albumin, pus and many granular and cell casts. Blood is always present, usually making the urine smoky or brownish red. In children there is a tendency to complete recovery.

Since the disease under discussion is preceded by acute infection elsewhere in the body the treatment naturally begins with the treatment or elimination of this infection. It is well known that the  $\beta$  hemolytic streptococcus plays an important rôle in acute nephritis which condition often follows acute streptococcal respiratory infections, scarlet fever and other disease in which this organism is present. Localized infections, such as otitis media, mastoiditis, osteomyelitis and erysipelas,

as well as the more generalized infections may be complicated by the development of nephritis. Another type of infection common in childhood and often disregarded as an antecedent to acute nephritis is impetigo contagiosa. In our experience many children with acute nephritis have had this as the only demonstrable preceding infection. Although the  $\beta$  hemolytic streptococcus more often than any other organism is implicated in acute nephritis, one must not lose sight of the fact that both the pathologic and clinical pictures of the disease can be produced by other organisms or their by-products, such as the  $\alpha$  streptococcus and the pneumococcus. Adequate care of these predisposing infections does much to prevent acute nephritis.

When there is a localized lesion, such as an abscess or acute otitis media, surgical treatment should be instituted. Adequate drainage of such an infection lessens the opportunity for the absorption of toxins and hence there is less likelihood of subsequent acute nephritis. The proper care of these infections may cause dramatic improvement in an already existing nephritis; thus the presence of kidney damage is indication for the radical treatment of such a localized lesion.

In recent years many sera have been developed for the treatment of streptococcal infections, and there is some evidence to show that in such diseases as scarlet fever and erysipelas their use is followed by a decreased incidence of nephritis. It would seem wise, therefore, to use serum in severely intoxicated patients suffering from scarlet fever or erysipelas. This same theory would apply to the use of serum in pneumococcal infections when the causative organism can be typed and found to belong to one of those groups for which adequate serum is available.

At present the whole therapy of streptococcal infections is undergoing a rapid change because of the introduction of a drug which seems to be more or less specific against this organism. This chemical, para-amino-benzene-sulfonamide, or sulfanilamide, if given in doses large enough to raise its concentration in the blood to between 5 and 10 mg. per 100 cc. causes the great majority of infections due to the hemolytic streptococcus to disappear rapidly. If the early optimistic reports on the use of this substance are borne out by later



investigations it will doubtless be a valuable aid in the prevention of acute nephritis as a complication of streptococcal infections. So far no one has demonstrated any harmful effects to the kidneys resulting from the use of this drug in therapeutic doses. Therefore, it seems reasonable to employ it even during the presence of nephritis if there is a coincident infection with the hemolytic streptococcus. When this is done it must be remembered that para-amino-benzene-sulfonamide normally excreted through the kidneys may be retained within the body and that its concentration in the blood may rise more quickly and to greater heights than it would if the kidneys maintained their normal excretory function. Therefore, the dosage should be controlled by frequent blood analyses with the purpose of maintaining a concentration near the therapeutic level and preventing the accumulation of the drug in the blood stream to the point of producing toxic effects, such as sulf-hemoglobinemia, hemolytic anemia, fever, acidosis and skin rashes. As yet no reports are available concerning the use of this chemical in acute nephritis.

In the enthusiasm for new therapeutic measures, particularly for things which seem to be specific, we must never lose sight of the fact that the normal processes of body defense and body repair should be fostered. *Vis medicatrix naturae* must ever remain a strong adjunct to any form of therapy, and there is no question but that good hygienic care, protection from exposure, proper nursing and carefully guarded convalescence during infections will lessen the likelihood of acute nephritis as a complication.

#### TREATMENT

In treating a child with a mild or average case of acute nephritis little more is needed than good nursing care. The prognosis is excellent when the condition is uncomplicated, and the vast majority of the patients recover quickly, completely and without sequelae. This happens under therapeutic régimes that vary tremendously. Rest in bed is important and should be continued as long as appreciable amounts of blood or albumin are present in the urine. Occasionally when convalescence is slow and a trace of albumin in the urine is the only remaining evidence of a preceding acute nephritis, it is

safe to allow the patient to be up and about if this increased activity does not cause a relapse or reappearance of other symptoms of the disease. A good deal of attention has been paid to the clothing and body heat of patients suffering from this disease. At one time it was considered wise to produce excessive sweating by the use of blankets and artificial heat. Later work indicates, however, that when water is eliminated by this route there is no appreciable loss of the abnormal toxic products and the chief effect, aside from making the child uncomfortable, is the loss of water needed for renal secretion. It is equally important not to allow the patient to become chilled as the resulting renal vasoconstriction may have the effect of intensifying the symptoms of the already existing nephritis. Children with this disease, then, must be clothed so that they are comfortably warm but not sweating.

The question of diet in the treatment of nephritis has provoked much study and many types of feeding have been tried, varying from virtual starvation of the patient for a period of many days to forcing a full diet with emphasis on proteins. The amount of protein given to patients with scarlet fever and other streptococcal infections bears no relationship to the occurrence of nephritis. Likewise, it is the opinion of many clinical observers that the quantity of protein in the diet during acute nephritis has little if any effect on the natural course of the disease. It has been our custom to give these children light, nourishing, easily digested food with no special limitation of protein, fat or carbohydrate but with no more sodium chloride than is necessary for palatability. During the first few days of the disease if nausea is present, no particular effort is made to make the child eat. An alkaline ash diet is considered beneficial by some. We have been unable to see any striking evidence of this but usually give fruit juices freely since they are well tolerated by young patients. In cases where the continued loss of albumin in the urine results in a lowered blood protein it is wise to increase the protein in the diet in an effort to recover this loss. This is especially true if the level of blood protein is low enough to cause edema. However, in acute nephritis this is rarely the case except where children have been on a poor diet for a long time or where the nephritis has advanced into the subacute or chronic stage.

The question of fluid intake has caused even more discussion than that of diet. There are two opposing points of view on this subject, those adhering to the one feel that fluids should be limited as much as possible in order to spare the kidneys additional work, and that the body, already edematous, has a sufficient reservoir of fluid to supply the blood stream and the kidneys with enough water for all the elimination of which they are capable. Others hold the opposite view that since acute nephritis is due to a circulating toxin secondary to some infection, the dilution of this toxin and its excretion are necessary before there can be an improvement in the capillary and hence the renal lesion and, following this, an increased ability of the kidneys to excrete. Adherents of this latter viewpoint believe in forcing fluids by mouth if possible, or by needle if necessary, to the point of several liters a day. It seems logical to adopt a more or less middle ground and to give these children a reasonable amount of fluid, probably very close to their normal intake, of from 1 to 3 liters a day. If there is nausea or loss of consciousness, making it impossible for the patient to take sufficient fluid by mouth, even in the presence of moderate edema, one should give intravenous glucose. This supplies to the blood stream both water for the promotion of renal excretion and glucose which furnishes a readily available food and prevents the ketosis incident to starvation. The glucose may possibly act as a detoxifying agent and also as a direct myocardial stimulant. Administration of physiologic saline is necessary only when there is a depletion of body electrolytes indicated by a low total base or low blood chloride.

Specific medication is not available, and again it is well to emphasize the fact that acute nephritis is primarily not an infection of the kidneys alone but a general systemic disease. It is unwise to use irritant diuretics in the presence of hemorrhagic nephritis. More harm is likely to follow their use than benefit to be derived from a slight temporary increase in the amount of urine excreted. When patients are uncomfortable it is safe and wise to give them an analgesic such as acetylsalicylic acid and for those who are restless, delirious or convulsive more powerful sedatives, such as paraldehyde, chloral or morphine may be used. Magnesium sulfate has been more valuable in the treatment of acute nephritis

than any other substance we have tried and we now give it to almost all patients with this disease. When there are no cerebral or cardiac complications and when there is no nausea it can be given by mouth in doses of from 5 to 25 Gm. every four hours, depending on the size of the patient. This can be kept up until there is a marked diarrhea or until the hypertension has decreased to within normal limits. If the drug cannot be taken by mouth, it is well absorbed by rectum in a 4 per cent solution or it can be given intramuscularly in a 25 per cent solution of the crystalline salt in doses of 0.1 Gm. per kilogram of body weight, from twice to six times daily depending on the severity of symptoms.

### COMPLICATIONS

The most serious complication of acute nephritis, if it can be called more than a severe symptom, is involvement of the central nervous system, with resulting restlessness, convulsions and coma. Hypertension almost always accompanies this group of symptoms. These manifestations of cerebral edema and irritation usually occur early in the disease and at times develop with great rapidity, so that careful observation and prompt treatment are most important. The aims of treatment are twofold; one, to decrease the cerebral edema and increased intracranial pressure as quickly as possible; and two, to lower the blood pressure which may be very high when this complication sets in. Lumbar puncture has long been used as a means of stopping uremic convulsions. Since the withdrawal of fluid below the edematous base of the brain may cause pressure on the medulla and result in respiratory failure, extreme care must be exercised in the performance of such a therapeutic puncture. Although it is a method of last resort it may be a valuable one but should be used with extreme caution. Occasionally good results follow the intravenous administration of hypertonic glucose. However, it is not unlikely that cerebral edema of an even severer degree may develop some hours later after the initial osmotic effect of the increased blood sugar has disappeared, so that the end-result is not always satisfactory. Again magnesium sulfate has proved to be a most valuable therapeutic weapon and seems to exert its effect both in decreasing the edema and relieving the general arteriolar spasm.

When convulsions are severe and intractable to the ordinary therapeutic measures, especially if the blood pressure is very high, magnesium sulfate may be given intravenously as a 1 per cent solution of the crystalline salt in quantities varying from 0.1 to 0.2 Gm. per kilogram of body weight. Extreme care must be exercised when the drug is used in this manner for both respiratory and circulatory collapse may occur. The blood pressure should be taken frequently while the fluid is run into the vein at the rate of 1 to 3 cc. per minute. As soon as a fall in systolic pressure of 10 to 20 mm. of mercury occurs or if the respirations become shallow or irregular administration should stop. It is important that calcium gluconate be available for immediate use as an antidote if symptoms of magnesium poisoning appear. The most satisfactory way to give magnesium sulfate is by intramuscular injection of a 25 per cent solution of the crystalline salt which may be given in doses of 0.1 Gm. per kilogram of body weight every four to six hours until improvement occurs or until the blood pressure descends to a normal level. As soon as improvement begins it is well to give the drug by mouth and stop the intramuscular injection. Sometimes sterile abscesses are produced especially when the fluid gets into the subcutaneous tissue. It is important to watch these patients carefully and to resume the more drastic treatment should convulsions recur, drowsiness increase, or a marked rise in blood pressure return. If the improvement in cerebral symptoms is accompanied by an increase in kidney secretion it is unusual to have a relapse.

The other serious complication of acute nephritis in childhood is myocardial failure, which is present to some extent in about 15 per cent of the patients admitted to the hospital with acute nephritis. It usually comes on after the nephritis has been present for several days and is manifested by an increase in edema, dyspnea, tachycardia, enlargement of the heart and the other well-known signs of heart failure. Here again, early treatment may prevent a fatal outcome. Hypertension is nearly always present in these cases, its sudden development being one of the principal reasons for failure of the heart muscle. therefore, it is important to lower the blood pressure as soon as possible. It is probable that spasm of the smaller arteries is an important causative factor, hence, the intramus-

cular administration of magnesium sulfate, as outlined above, should be instituted at once, and continued until the blood pressure becomes normal or, at least until cardiac compensation is reestablished. We have found it helpful to give these patients hypertonic glucose by vein every few hours, an average dose being 50 cc. of a 20 per cent solution, given over the course of fifteen to twenty minutes. Digitalis has also been valuable but it must be remembered that since the kidney excretion is diminished the usual rules for digitalization may not hold. One must proceed with great caution in administering the drug, being constantly on guard for the appearance of toxic manifestations. One child under our care was given less than his calculated digitalizing dose and continued to have signs of intoxication for five days after the drug was stopped. Morphine in full doses often helps to quiet these children. The presence of cyanosis is an indication for oxygen, and we have seen extreme restlessness in a cyanotic child relieved more quickly by oxygen than by all the other means mentioned above. Venesection with the removal of from 100 to 200 cc. of blood may be followed by a dramatic improvement and may allow sufficient time to institute more permanent therapeutic procedures.

It must be remembered that when the heart fails in the presence of acute nephritis the patient is in a serious condition where every means at hand must be used to break the vicious circle. As much as we would like to test the efficacy of a single drug or the relative value of different drugs in treating this complication we are not justified in omitting those tried and proved measures for the relief of a failing heart. Delay may mean death, and a break in the progressive train of symptoms usually points toward complete recovery.

After a child has recovered from acute nephritis it is well to be sure that any existing foci of infection, particularly the tonsils and adenoids, are eliminated. It is also wise to give such a child additional bed rest during respiratory and other infections which may occur in succeeding months, and protect him from undue exertion and exposure.

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### PROGRESSIVE BIRTH PALSIES

THE term "cerebral birth palsy" is neither a clinical nor a pathologic entity. This term is one used in common for a great number of cerebral pathologic conditions which occur before, during or shortly after birth, and in which some type of motor defective state is found.

The cerebral palsy consists of three major symptoms; namely, palsy, mental manifestations and epilepsy. By "palsy" there is implied a motor deficit involving the pyramidal or extrapyramidal pathways. The former results in pareses or plegias, the latter in chorea, athetosis, etc. The mental picture varies from normal, through a slight diminution of the intelligence quotient to complete amentia. Grand mal seizures occur in about 60 per cent of all cases. They may appear shortly after birth or for the first time many months later.

Many clinicians believe that these birth palsies are caused by hemorrhage or trauma in the newborn. There is often a vague association of the motor defective state with Little's disease. If one is to adhere strictly to the clinical picture as described by Little,<sup>1</sup> then it should be applied only to those cases of cerebral diplegia associated with asphyxia in difficult labor.

This author, in 1853, suggested that difficult labor might be an etiologic factor, but stated that lack of development of the cerebral tissues and meningeal inflammatory processes were the usual causes. Nine years later in a second paper, he stated that nearly three fourths of all cases of spastic cerebral paralyses were caused by intracranial hemorrhage at the time

of birth. He stressed the factors of "birth pressure and intermittent placental respiration."

In 1885, Dr. Sarah McNutt<sup>2</sup> reported a case which she termed "double infantile spastic hemiplegia," the labor difficult and prolonged. A second case report followed in which she generalized meningeal hemorrhage as the cause of all infantile spastic states which dated from the time of birth, and which were associated with difficult labor. Thus Dr. McNutt corroborated the work of Little, and although it has since been shown that she misinterpreted her pathologic observations, and in spite of the numerous contributions to the literature on these cerebral palsies, her teachings have become more or less universally accepted.

Sigmund Freud,<sup>3</sup> 1897, in his monograph proved conclusively that these infantile palsies did not have intracranial hemorrhage as their one common etiologic factor. On the other hand he emphasized too strongly the rôle played by poroncephaly. In 1924 J. Collier<sup>4</sup> maintained that they were all due to a "primary degeneration of the cerebral pyramidal neurones."

These several widely divergent points of view selected from the innumerable contributions to the literature emphasize the striking lack of uniformity in opinion as to etiology and pathologic background, and it is evident that the cerebral type of palsy is not a clinical or pathologic entity.

In the fall of 1932, the author<sup>5</sup> published a paper entitled, "Cerebral Birth Palsies; a contribution to their pathology with a report of a hitherto undescribed form." In this paper, a peculiar progressive cerebral degenerative process was shown to be the background for the clinical picture of a cerebral birth palsy. Keeping in mind the fact that we were not dealing with a stationary cerebral state or scar, the end-result of a previously existing cerebral pathology, but instead with a clinical syndrome which showed evidence of progressive activity, it occurred to us that if we searched carefully enough, we might find among the protean pictures seen in these palsies, cases which might show evidence of clinical activity.

During the past several years, since the study of the autopsy in the above-mentioned case, a series of these defective motor states have been observed. Of these, the several



following have been selected for the purpose of showing progression of symptoms and signs.

The following cases are typical instances of clinical progression. Motor signs may be so slight as to be easily overlooked. If very obvious at birth, the attention of the parents and attending physician is brought immediately to this motor condition. On the other hand, the slow but gradual increase in severity of motorium involvement is such as to be easily overlooked, and only observation over a longitudinal span of months, rather than at any one cross section of the child's life will indicate that the motor disorder is becoming progressively worse.

Moreover, involvement of the basal ganglia pathways may be superimposed upon a pyramidal tract disorder. The reverse may take place, and the disturbance in plastic tone, such as is found in athetosis, may mask the hypertonicity of early cortico-spinal pathway disease. Instead of definite involvement of a limb or extremity, speech might be the cerebral sign of motor disorder. Speech defects (stuttering), with left-handedness, are so frequently associated that this combination is no longer looked upon as mere coincidence. Clinicians recognize the fact that stuttering in a left-handed child becomes worse if the child is forced to be dextrmanual. We have seen several instances of this combination of stuttering in left-handed infants eventually develop into right hemiparesis. This indicates the fact that both the speech and left-handedness must together be considered as signs of defective left cerebral functioning.

The author considers cases of left-handedness, especially when associated with stuttering, as potentially epileptic, for this sequence also has been noted in several instances. The convulsion may occur at or shortly after birth, followed later by motor defect, mental retardation or both. Is it not logical to assume that the same disease which produces the mental signs and convulsions, may spread and affect the motorium? Need the motor signs be present from the very beginning? In the opinion of the author, this prerequisite is essential only from one standpoint and that is purely nosologic; because the same degenerative process may affect any part of the brain and bring about any possible variation in the sequence of clinical

progression. In many of the degenerative cord disorders and system diseases, the usual accepted sequence need not follow classical lines. For instance, amyotrophic lateral sclerosis may begin as a progressive neural atrophy, eventually showing the development of pyramidal tract involvement. Bulbar signs may even precede both the above.

This same clinical variation may occur in the cerebral palsies, in that other phenomena might antedate the motorium signs.

In the selection of these following case reports, only those were used which fulfilled these requirements:

1. Multiparous mother, without instrumentation or prolonged labor, so as to eliminate the factor of trauma to the newborn.

2. Infrequency of convulsions. It is more or less generally accepted that frequent convulsions tend to mental deterioration. Assuming this fact as true, although it has not been corroborated pathologically, nevertheless care was taken to eliminate this factor.

**Case I.**—Normal delivery, mother multipara 4. The family and past history essentially negative. This girl was first seen at the age of four. She was brought in because "she seems clumsy, falls frequently, and is becoming left-handed." The mother states that she did not begin to walk until she was about fourteen months of age, and at a year and a half began to drag her right leg. The mother added, "she never used the right side as much as she used the other. This right leg is getting worse and it's getting thinner. She is just as smart as my other children, but lately, she seems to be getting nervous and irritable and has developed a temper. In the past several months she has voided in bed at night." The history shows that "this child was right-handed at first, but began to use her left hand about six months ago, and now she even eats with her left hand."

The mother was told to keep her under close observation for nocturnal enuresis. It was shown that occasional epileptic episodes occurred at night.

Examination showed a moderately well-nourished and well-developed girl. The somatic musculature was normal, except for slight atrophy of all the muscles of the entire right lower extremity. There was no shortening, but the examination showed a definite motor weakness with a slight increase in muscle tonus. Plantar stimulation produced slight dorsal flexion of the great toe and a tendency to fanning of the smaller toes. All deep reflexes were more active on the right. The mental age was normal, and although this child was alert and cooperative, her misbehavior and psychomotor restlessness were striking. "The temper tantrums are unprovoked and seem to arise for no apparent reason" (psychic equivalent?).

*Sequence.*—Motor (pyramidal tract) defective state, followed by epilepsy and possible early mental manifestations.

**Case II.**—R. M. M., aged fifteen years. Normal delivery, multipara 5. The family history negative. Siblings normal.

After this boy was born it was noticed that he had a peculiar rolling movement of the eyes. Between four and six weeks after birth, the mother stated he did not move the right arm as freely as the other. This weakness gradually progressed, and at four years of age was completely paralyzed in the right upper extremity. At that time he had begun to show signs of weakness in the right leg, and because his attending physician thought that his condition was due to a "blood clot on the brain" a trephine over the right Rolandic region was done but no clot was found. Had several convulsions during the year following the operation, but none since.

He began school at seven. There were repeated failures, and at fourteen he had reached the third grade of a parochial school. Since then he has been selling papers, contributes to his family, and although he appears rather stupid and dull with his I. Q. of 68 he is really likeable and quite cooperative.

The examination shows the following significant findings:

A classical left brachial monoplegia, with marked shortening and spasticity of the fingers in extreme flexion contraction. There is a moderate degree of atrophy of the left lower extremity with typical pyramidal tract signs. The right side of the body is normal.

*Sequence.*—In this case there is a history of progression of right-sided pyramidal tract disease. There is, in addition, a mental retardation associated with epileptic phenomena.

**Case III.**—A six-year-old boy, brought in by his mother who states that "he is my fifth child; he never seemed as bright as any of my other children. He has always had a slobbering of the mouth. He was two years old before he began to walk and he never learned how to talk; never got over that St. Vitus' dance he got when he was less than a year old. At about four months after he was born, he had a convulsion. He was constipated at that time, but he didn't have fever and he didn't look sick. After the doctor gave me some medicine for his bowels (milk of magnesia), he never had any more convulsions. As he grew older, up to five, the jerks grew worse, and then he began to get those twisting movements like he is now. The visiting nurse told me I ought to send him to Rosewood (an institution for feeble-minded) but I didn't want to send him there until I was sure nothing else could be done."

Two months ago he began to have daily grand mal episodes. The mother stated, "since he has been taking your medicine (bromides) the spells aren't so bad but those jerky twisting movements are the same as ever."

Examination shows this youngster to be oligophrenic. Continuous chorea and occasional athetoid movements, mostly present when standing or lying down. There is a definite diminution in plastic muscle tonus, permitting excessive stretching at the joints. This corresponds to the classical picture of chorea as described by O. Foerster.\* At other times during the athetosis there is a marked increase in plastic muscle tonus.

*Sequence.*—An amentia, followed by motor manifestations of an extrapyramidal type, with onset of epilepsy at six. There is progression of chorea to athetosis, a possibility described by A. Jakob.<sup>7</sup>

**Case IV.**—An eleven-year-old colored girl seen in the neurologic outpatient service of the Provident Hospital. A multiparous mother,<sup>6</sup> who is intelligent and cooperative. The patient was the third born. No history of difficult labor or instrumentation. This child had spasms shortly after delivery; these continued for about six months, ceased, and at three years of age she had one seizure. The mother states that "she never used her left arm the way she should, but when the spasms stopped, the arm got worse and then she began to have trouble with her left leg." She began to walk at two and one-half, and started to talk at the same time. At about three years of age, when she began to get about fairly well, the mother observed that "both of her legs, especially the left, seemed stiff. The right leg began to get bad when she was about seven, nearly eight, and lately, both arms are like that."

The examination shows a moderately well-nourished colored girl, whose appearance does not suggest her low mental age (six years). The neurologic status—a typical spastic diplegia (tetraplegia), with marked hypertonicity and the classical pyramidal tract involvement signs. The gait is typically scissors type. The blood and spinal fluid are negative.

*Sequence.*—Convulsive seizures in a mentally deficient girl but with striking progression of pyramidal tract involvement.

**Case V.**—Five-year-old boy, the third of 5 children, brought in because of difficulty in walking. The family history is negative, except for a male sibling who died shortly after birth (cause not known). The mother first noticed that his locomotion became increasingly difficult at about three years of age. Any attempt to stand was attended by marked increase in extensor tonus of both extremities, the youngster standing on his toes. At five years of age, this boy had progressed into a typical spastic diplegia. About eight months ago "the trouble began in his arm, in that he failed to use the left arm as much as he did formerly."

Examination showed in addition to classical diplegia, hyperactive deep reflexes with Hoffmann's sign in the right and a supranuclear type of right-sided facial involvement. There are no convulsions, nor is there any impairment of mental age.

*Sequence.*—Progression of pyramidal tract symptomatology without epilepsy or mental change.

#### COMMENT

These cases have been selected from a series of 34 observed during the past several years. Pyramidal or extrapyramidal tract types of motor disturbances are common to all. The motor changes may be obvious at the time of birth or may have first been noticed many months later. In several of the cases there is definite intelligence deficit. This is brought to the

attention of the mother usually at about the second year. chiefly because the child has failed to learn to talk. Convulsive states are almost a constant accompaniment, so much so as to be accepted as an integral part of the syndrome.

The most widely accepted theory as to the etiologic factor is birth injury, with either intracranial trauma or hemorrhage. Schwartz<sup>8</sup> found hemorrhage and softening in 65 per cent of 300 cases. Cornwall<sup>9</sup> discussed meningeal intracerebral and subdural hemorrhage, as well as sinus thrombosis as causes of infantile palsies, stressing subdural hemorrhage incident to tentorial tear as causing extravasations of blood into the soft brain substance.

Another widely accepted theory is that these palsies are caused by poroncephalic defects. There is considerable discussion as to the nature of the poron or cavity formation. It is traumatic. Jaffee,<sup>10</sup> secondary to a polioencephalitis (Sachs and Peterson<sup>11</sup>); according to Heschl who, in 1859, first introduced the term of "poron," considered them as due to either faulty development during intra-uterine life or to retrogressive changes incident to vascular occlusion (quoted by Schob<sup>12</sup>). J. H. Globus,<sup>13</sup> in 1 case, thought that it was due to a prenatal encephalitic process which progressed after birth.

Collier<sup>14</sup> maintained that these palsies are due to a "primary degeneration of the neurones," but those who work in neuropathologic laboratories have seen the clinical picture of cerebral birth palsy in such widely varied pathologic states as congenital maldevelopments, amaurotic idiocy, infantile cases of diffuse subcortical sclerosis belonging to the group of per-axialis subcorticalis diffusa.

There are also purely degenerative conditions in which the bulk of the pathology lies within the cortex; affecting chiefly the upper cortical layers. Cases of this type were described by Spielmeyer,<sup>15</sup> Bielschowsky,<sup>16</sup> Jakob,<sup>17</sup> and Hostermann,<sup>18</sup> under the caption of "Intracortical Hemiplegia" or "Hemiplegie bei intakter Pyramidenbahn."

Papers by Henschen<sup>19</sup> and Schaefer<sup>20</sup> indicate the relationship of vascular disorders to these birth palsies. Congenital anomalies of the nervous system might also produce this picture.

It is logical to assume that an early destructive lesion could

cause either some interference in myelinization or maturation of cerebral substance, but when these disorders have formed a scar the latter cannot possibly account for clinical progression. The duration of secondary degeneration of cerebral axones, from the inception of its end-stage, is approximately nine to ten months. Whatever signs of activity there might be, could logically be explained on this basis only during the first year.

### CONCLUSION

There are among the great group of cerebral palsies in infants, cases in which clinical progression indicating an active process may be noted if care is taken in anamnesis to obtain all the actual facts in chronologic sequence of the course of the disease.

The object of this paper is to direct attention to processual or progressive cerebral disorders. The presence of clinical activity should indicate the possibility of a degeneration of cortex and deeper lying structures, perhaps in the nature of the pathology similar to that seen in the author's<sup>5</sup> case report.

We must keep in mind the fact that degenerative diseases may show activity over many years.\*

Unfortunately, the demonstration of progressive activity does not reveal the nature of the underlying pathology, but it is certainly of value in emphasizing the fact that one is not dealing with a stationary or nonprogressive lesion, thereby eliminating such factors as trauma, hemorrhage and maldevelopments.

From this standpoint the approach to the therapy of certain palsies is obviously not only an orthopedic one, but must find its solution in medicine, rather than in surgery.

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### TREATMENT OF SYPHILIS IN INFANTS

THE treatment of congenital syphilis in infants is almost always a serious problem, complicated as it is by several factors not encountered in adults. One or more of these factors always play a part in the treatment.

Of first importance is the fact that these infants cannot be reasoned with, and cannot understand the necessity of being subjected to regularly administered pain and annoyance.

Secondly, the best treatment, according to our present knowledge of syphilotherapy, requires "needle" treatments which always, even with the most efficient technic, cause pain.

Thirdly, the vast majority of congenitally syphilitic children are born of parents of a low stratum of society, frequently ignorant, who themselves rarely understand the full implication of the disaster which has befallen them and their offspring, and who frequently cease not only their own treatments but those of the child, because they cannot tolerate the baby's crying when it is hurt by the needle.

Finally, and of extreme importance, is a consideration of the parents' financial status and, often, of their inability to pay for their own treatments and for those of the infant. Treatments, even at 25 to 75 cents each, become in many instances a hardship, and in explanation of their lapse in treatment, they say that it is easier to do without treatments than without food.

These problems must be met, and every effort made to overcome them through an understanding social service department and a considerate, able physician, properly trained in the technic of the administration of the drugs.

The parents must be consoled, and constantly reminded that without this treatment the infant may never attain a condition of normalcy; nor must the physician permit his staff to become irritated or annoyed by the crying infants; this may lead to careless work and indifferent handling of the case. Their care is a duty we have to perform to the best of our abilities and we should never lose the sympathetic feeling for these unfortunates.

#### THE DRUGS USED

There are four types of drugs which we use in the treatment of congenital syphilis: arsenic, bismuth, mercury and the iodides.

Sulfarsphenamine, a trivalent arsenical, is the form in which arsenic is usually administered. It is the only arsphenamine that can be administered intramuscularly with very little pain or consequent induration. This is of extreme importance because, up to the age of two years, venipuncture, while possible and regularly practiced by us in obtaining blood for serology, is not feasible as a means of giving treatment. As a consequence, almost all therapy to infants is by intramuscular injection. It has been advised that the dose be measured by weight<sup>1, 2</sup> of the infant and that this dose should be approximately 10 to 20 mg. per kilo of weight. We have not always found this a desirable means of computing the dose because of reactions; therefore, as an arbitrary dose, we give infants up to three months of age, of an average weight, 0.025 Gm.; from three to six months of age, 0.05 Gm.; and from six months to one year of age, 0.1 Gm. Concentration of solution is of importance also, and the more concentrated the solution, the less pain is experienced; the dilution of 0.5 Gm. in 1 cc. is preferable and the dose can easily be gauged by a tuberculin syringe.

In late congenital syphilis it is preferable, where intravenous injections are possible, to use neoarsphenamine (in a dilution of 0.1 Gm. in 2 cc.), or silver arsphenamine (in a dilution of 0.1 Gm. in 5 cc.), instead of sulfarsphenamine. In white patients, silver arsphenamine must be used cautiously as it can cause a peculiar leaden-colored type of argyria. One may use it in negroes without concern as such discoloration cannot be noted. In the older children we have found these

drugs to be more effective and less reactive than sulfarsphenamine. In these older children, we disregard the rule of dosage by weight, which is usually prescribed as 10 mg. per kilogram of weight, and generally administer to children, of average weight, from two to four years of age, 0.1 Gm. to 0.2 Gm. of neoarsphenamine, or 0.05 Gm. to 0.1 Gm. of silver arsphenamine; and from four to ten years of age, 0.25 Gm. to 0.3 Gm. of neoarsphenamine or 0.1 Gm. to 0.15 Gm. of silver arsphenamine.

Under certain conditions, specifically where "needle" treatments are inadvisable, due to extreme terror or "nervousness" of the patient, one may administer stovarsol (acetarsone) by mouth. This drug, given by mouth, is spirocheticidal, destroying surface organisms generally within twenty-four hours; but, as it is a very toxic drug, frequently causing dermatitides and also increasing the icteric index, it should be administered with great care, never letting the guardian have more at any time than is sufficient for three days' to one week's treatment, and cautioning the guardian about the drug's toxicity; that is, impressing upon the guardian the need for reporting to the attending physician any reactions, such as itching, skin eruptions, yellowing of the skin and eyes, diarrhea, etc. The dose of this drug is approximately 0.1 to 0.25 Gm. daily for two weeks, followed by a rest period of one week, using mercury inunctions during this interval.

Bismuth is the next drug in point of usage and has almost completely replaced mercury. In our experience bismuth subsalicylate (18 to 20 per cent suspension) has proved an effective drug, causing little pain if properly injected. In place of this, one may use a bismuth preparation soluble in oil or one soluble in water. The dose of bismuth subsalicylate as prescribed by us is, to infants up to six months of age, 0.05 Gm.; from six months to four years of age, 0.1 Gm. In our experience these comparatively large doses have been well tolerated without skin, gingival, or other reactions.

Mercury, although the oldest drug in point of service, is not used as often as bismuth. Rarely, in patients whose disease is resistant and does not respond to sulfarsphenamine or bismuth, mercury inunctions have accomplished the desired results. Unguentum hydrargyri, 30 to 50 per cent, is the

preparation of choice and about  $\frac{1}{2}$  to 1 drachm is used once a day, either by rubbing the ointment into the skin or by putting it on the belly band and permitting the actions of the infant to rub it in.

The iodides are rarely used in our clinic, as they are of no use in early syphilis and of little use in late congenital syphilis. If and when used, we prescribe the saturated solution of potassium iodide, giving rather large doses (as compared to adults), namely, 5 to 10 drops three times a day.

#### PLANS OF TREATMENT

In order to rationalize our system of treatment of syphilis in infants, we have grouped our plans of treatment under the following headings:

Preventive (prenatal care and treatment).

Curative (in early congenital or acquired syphilis).

Arrestive (in late or tardive congenital syphilis).

Supportive.

**Preventive Treatment.**—There can certainly be no questioning the statement<sup>3, 4</sup> that the supreme method of treating congenital syphilis is to prevent it. To do this we must utilize every instrument and method at our command to detect syphilis in the pregnant woman. There have been loud and foolish outcries against performing routine serologic tests for syphilis (Wassermann tests and flocculation tests) on pregnant women, some physicians insisting that this was prying into the private affairs of good women. Unfortunately, occasionally such physicians have had to dishonestly explain away an infected, macerated infant, miscarriage, or full term syphilitic child. Williams<sup>3</sup> was among the first to show that adequate antisyphilitic treatment administered to the expectant mother was ample assurance of a live infant, often entirely free from the disease. McKelvey and Turner<sup>1</sup> reported that if treatment were given as late as the eighth month and carried through to delivery, life expectancy was markedly raised. Our experience has confirmed these findings, and it is indeed rare to report the birth of a syphilitic infant, if treatment is begun in the expectant mother between the fifth and six months. Such treatment consists of alternating series of weekly injections of one of the arsphenamines, intravenously, and a bismuth prep-

aration, intramuscularly. That is, an arsphenamine treatment (arsphenamine 0.3 to 0.4 Gm., or neoarsphenamine 0.6 Gm. or mapharsen 0.06 Gm.) is given once a week for eight weeks. Then, without a rest period, the patient receives weekly injections of a bismuth preparation for eight weeks, and these alternate series of injections are continued until delivery and are resumed as soon as practicable after delivery until the patient has received one and one-half years of consecutive weekly treatments. If the syphilitic infection is not detected until the sixth or seventh month, it is desirable to administer the first few treatments of bismuth and an arsphenamine (about four or five) concurrently, or if the interval between the commencement of treatment and delivery is only between eight and twelve weeks, we have noted better results by administering both the arsphenamine and bismuth drugs concurrently until delivery. It should be emphasized, however, that even 2 or 3 treatments of arsphenamine and bismuth, administered concurrently immediately before delivery, will noticeably raise life expectancy. To accomplish the best results, treatments should be begun as early in pregnancy as possible, and that can only be brought about by the routine use of the serologic tests for syphilis (the Wassermann or complement fixation and the flocculation or precipitation tests) for the detection of the disease when otherwise unrecognizable. In the "best" stratum of society, syphilis is present to the extent of 1 per cent, and in others, the percentage ranges from 7 to 30 per cent. It is a misfortune to be afflicted with this disease and a large proportion who are so afflicted have contracted it innocently. Therefore a greater effort must be made to prevent the transmission of the disease to the offspring, most innocent victim of all.

It is questionable whether a woman, adequately treated before, or during and after one pregnancy needs to be treated during each succeeding pregnancy. In most instances I have found it to be unnecessary, provided the patient has not become reinfected.

**Curative Treatment.**—Infants acquire syphilis from external sources, either genitally or extragenitally. Those infected genitally are usually victims of a superstition, principally among very ignorant negroes and whites, that if he (it is al-

most always a male) can have coitus with an infant of any sex or a virgin he will transfer the disease to the other party and be himself cured. Most of such transferred infections have been in negro infants. The most frequent infection extragenitally, in our experience, has been on the lips from kissing; of the latter, one interesting case may merit report: asked to see an infant eight months old because of a lesion on the upper lip, we found this lesion to be a chancre and demonstrated *Spirochaeta pallida*. Everybody except the mother was suspected, as her blood Wassermann and examination had been negative before and immediately after delivery. But as all other contacts were negative, the mother was reexamined and found to have early secondary syphilis, Wassermann positive. She had contracted the disease from her husband, after the birth of the child, and in kissing the child had infected it.

As the treatment of acquired syphilis and early congenital syphilis in infants is the same, these will be considered together. To accomplish a cure in early congenital syphilis, it is necessary to detect the presence of the disease at the earliest possible moment, preferably before the age of two months, and to treat intensively.

There are those who contend that all infants born of syphilitic mothers should receive a full course of antisyphilitic treatment, even though no evidences of the disease are detectable in the child, and regardless of whether or not the mother has received adequate antisyphilitic treatment. This is a difficult question to decide, but as, in our experience, so many infants born of adequately treated syphilitic mothers remain apparently free of the disease, clinically and serologically, it seems unnecessary to torture those who are nonsyphilitic and do not require treatment, in order to make sure that every syphilitic infant may receive necessary treatment.

As a rule, we have required a definite diagnosis of syphilis before instituting treatment. The history of syphilis in the mother has aroused our suspicions concerning the child, and repeated, consistent efforts have been made to confirm this suspicion to certainty or to completely remove the stigma.

It is required of those attending deliveries that all placentas from syphilitic mothers be carefully examined histologically for evidences of the disease. Cord blood is no longer examined

as it was shown by Fildes<sup>5</sup> not to be indicative of syphilis in the infant. From the work of Cooke,<sup>6</sup> Dunham,<sup>7</sup> and Faber and Black,<sup>8</sup> it is to be noted that a positive blood in the infant that reduces in titer week by week is probably only a "carry over" from the mother and not indicative of syphilis in the infant. All such positive bloods are followed by weekly blood examinations until proved either conclusively positive or negative. It is much better to wait a little longer, until the serology is definitely and persistently positive before embarking on one and one-half to two years of "needle" treatments. It has lately been shown by Caffey<sup>9</sup> that the chondro-epiphyseal lines demonstrated by roentgenograms, formerly believed to be syphilitic, are now known to be due frequently to a bismuth deposit absorbed from the mother's treatment.

In the final analysis the infant's blood, therefore, remains the most reliable indicator as to the presence or absence of syphilis, and repeated examinations should be made in the early weeks of the infant's life, in the effort to diagnose the presence of syphilis as early as possible, preferably by or before the second month of life. Of course, if any lesions are present, such as bullae, papules, erosive lesions (mucous patches or condylomata lata) no further confirmation of the diagnosis is required than a dark-field examination demonstrating *Spirochaeta pallida*. Treatment begun at this early date and continued for a period of twenty-four months will insure a cure in a large majority of the cases.

The treatment consists of alternate series of weekly intramuscular injections of sulfarsphenamine (15 mg. per Kg. of body weight has been prescribed, but our dosage is arbitrarily usually 0.025 Gm. to infants of average weight, up to four months of age; 0.05 Gm. for infants from four to eight months of age; and 0.1 Gm. for those from eight months to one and one-half years of age), and bismuth subsalicylate in oil (also intramuscularly, 0.05 to 0.1 Gm.). Treatment is continued until the serology is negative and all clinical evidences have disappeared, and for one year thereafter, usually constituting one and one-half to two years of consistent, consecutive weekly treatment, *without* rest periods, unless lapses in treatment are mandatory due to the unsatisfactory condition of the patient.

Before discharging the patient on probation, the cerebrospinal fluid should be examined. Observation should be continued for years, preferably to adulthood. It is doubtful whether a "cure" will prevent the appearance of the stigmata usually seen in late congenital syphilis.

**Arrestive Treatment.**—Opinions differ as to whether treatment will prevent the appearance of clinical evidences of the disease. Igersheimer<sup>10</sup> asserted that, with or without treatment, both cornea were almost invariably involved, sooner or later. On the other hand Carvill and Derby,<sup>11</sup> and Robinson,<sup>12</sup> found that adequate treatment, instituted when the interstitial keratitis involved only one cornea or neither, prevented the infection from appearing in the other cornea, or at all.

In all patients in whom it is permissible, we administer alternate series of either arsphenamine, neoarsphenamine, mapharsen, or silver arsphenamine, intravenously, and bismuth subsalicylate intramuscularly. As previously mentioned, caution is necessary concerning silver arsphenamine, which may cause a peculiar leaden-colored type of argyria if used for more than two series of eight injections. It is preferable therefore to use this drug carefully *or* only in negroes.

In this stage of the disease (late congenital syphilis), treatment should be continued from one and one-half to two years and then terminated, the patient being told to report once a year for a physical examination and blood test. The serology is almost invariably positive at the end of treatment and will probably remain so as a Wassermann fast reaction. I have known such patients to receive from some physicians consecutive weekly treatments for five years or more without change in the serology. Further treatment may be given once a year or once in two or three years, amounting to one or two series each of a bismuth and an arsphenamine at these periodic visits.

Although reactions are not common in early congenital syphilis, they are encountered with moderate frequency in the late type of the disease. The immediate or slightly delayed reactions are usually only annoying and of little moment, but the delayed reactions, especially the dermatitides, jaundice and the blood dyscrasias, should be kept foremost in mind and the patient or guardian questioned at each visit before a treatment.



Even a suspicion of such a reaction warrants temporary (and occasionally permanent) cessation of treatment with the arsenicals. Reactions from bismuth are rarely severe enough to contraindicate further use of the drug.

**Supportive Therapy.**—In those patients with late congenital syphilis who have developed certain destructive manifestations, methods of treatment other than antisyphilitic are required in addition to the regular treatment.

If both corneae are involved and a thick opaque obstructive scar has formed, arsphenamine, bismuth, mercury or iodide treatment is generally ineffective, and, aside from preventing other lesions from forming, is valueless. In our experience old corneal opacities have not been affected or resolved under such treatment. These patients should also be seen and treated by the ophthalmologist. It is possible that, expertly applied, radium or roentgen-ray therapy may be effective in removing or thinning the opacity. This, however, is best judged by the ophthalmologist.

Eighth nerve deafness, when it does occur, has never been relieved in our group of cases. One can only hope that adequate treatment of late congenital syphilis will prevent the occurrence of this manifestation. The otologist, by proper appliances, may aid the patient to put what little hearing is left to the best purposes.

The patient with central nervous system involvement will frequently obtain good results if his condition is detected before the symptomatic phase occurs. Malarial infection therapy (which is our choice) or any other fever-producing apparatus should be used until an adequate number of peaks of temperature have been obtained; this is usually twelve to fifteen; more peaks are desirable if procedures other than malaria inoculations are utilized.

We have used tryparsamide in some of our older patients with very good results, but this should be used only in those cooperative patients in whom a visual field examination can be obtained and only in patients who are believed intelligent enough to complain or tell of dangerous premonitory symptoms, suggestive of amblyopia.

In those patients with central nervous system involvement who have become symptomatic of paresis, commitment to a

hospital for the insane is advised. There, adequate treatment can be given, and if the patient recovers he can be released to continue the necessary adjunct treatment. But if treatment is not effective, he will be where he can receive better attention than anywhere else.

Finally, it should be stressed that to treat the patient is of far greater importance than to treat the disease, and that the wisest admonition is to keep both factors equally and continuously in view.

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## CLINIC OF DR. NICHOLSON J. EASTMAN

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### HEART DISEASE IN PREGNANCY: THE RESPECTIVE DUTIES OF INTERNIST AND OBSTETRICIAN

THERE is general agreement that cases of heart disease in pregnancy are best handled by the obstetrician and cardiologist in close operation. In no other complication of gestation does the obstetrician hang so heavily on the statement of the internist or hazard so much on his advice. Accordingly, it would seem appropriate to outline a few of the facts which the obstetrician expects from the cardiologist in a case of heart disease complicating pregnancy, and at the same time to delineate what seem to me the main responsibilities of each in this important relationship.

The first fact which the obstetrician will want to know is whether the woman has rheumatic heart disease. It will be recalled that several of our standard criteria of heart disease become invalid during pregnancy. Apparent cardiac enlargement, systolic murmurs, accentuation of the pulmonary second sound, shortness of breath on exertion and even crepitant râles at the base of the lungs may be present in pregnant women who have perfectly normal hearts. The diagnosis of heart disease in pregnancy is rendered still more difficult by the mammary enlargement which occurs, a change which makes percussion less reliable and hampers auscultation over certain areas.

The two alterations in the heart during pregnancy which most frequently simulate disease are the change in cardiac outline and the occurrence of murmurs. The former is due in part to mechanical factors, namely, the growing uterus and elevated diaphragm, and in part to an actual increase in the

total area of the cardiac outline. During the last months of pregnancy the growing uterus pushes the diaphragm upward with the result that the heart is displaced to the left, superiorly and somewhat in the direction of the anterior chest wall; at the same time a certain degree of rotation of the heart is believed to take place. These changes are not constant either in degree or direction and vary according to the size and position of the child, the amount of amniotic fluid, the strength of the abdominal muscles and the constitutional type of the thorax. It must also be noted, moreover, that superimposed upon these changes there occurs another and perhaps equally important one and that is an increase in the total area of the cardiac outline. Basing his figures on roentgen ray measurements, Gammeltoft, in 188 cases of pregnancy with no cardiac disturbance, found an increase in the longitudinal as well as the transverse diameter of the heart in 23 cases as early as the fourth or fifth month. This increase became more frequent in the sixth and seventh months, when the longitudinal diameter was increased in 39 cases and the transverse in 33. These measurements were taken at a time when the upward pressure of the diaphragm was of no particular consequence. The roentgen ray studies of Walter Frey are still more convincing. He found among 25 women who were between three and four months pregnant that the transverse diameter of the heart was increased more than 0.7 cm. in 21 cases, or in 84 per cent; while in 10 cases, or 40 per cent, a similar augmentation of the longitudinal diameter was observed. In Klasten and Palugyay's study of 33 normal pregnant women, it was found that the distance from the midline of the sternum to the left margin of the heart was increased on an average 13 mm., and to the right margin of the heart, 3 mm.; these changes were due in part to the shift in the position of the heart and in part to an increase in its apparent size.

Whether hypertrophy or dilatation is the cause of the increase in cardiac outline which occurs during gestation is a moot question. At best, however, the problem is an academic one. From a practical standpoint of view, the conclusions to be reached from these investigations are clear. During pregnancy, as the result of the upward pressure of the diaphragm and the increase in the diastolic size of the heart, the positional

relationships of the heart in the thoracic cavity are frequently changed. The apex beat is moved outward and upward. The left cardiac wall is displaced to the left, a distance which averages about  $\frac{1}{2}$  inch but which may reach almost 1 inch. Therefore, the attending physician must be cautious about making a diagnosis of pathologic cardiac hypertrophy in pregnancy unless it is evident that he is dealing with a very large heart.

The other common alteration in pregnancy which may suggest heart disease, namely, the occurrence of murmurs, is present in from 10 to 20 per cent of gravid women. Various theories have been promulgated to account for these "functional" or "accidental murmurs," none of which are altogether satisfactory. The explanation advanced by Rumpel and Reicher, and subsequently endorsed by Frey, seems perhaps the most reasonable. These authors call attention to the fact that these murmurs do not make their appearance until late in pregnancy, often disappear within a day or two after delivery, and accordingly are to be most logically associated with upward pressure of the enlarging uterus upon the diaphragm and in turn upon the heart. They note also in this connection the observation of C. Gerhardt upon the occurrence of systolic heart murmurs in cases of ovarian cysts; this author not only observed such murmurs, but found that they disappeared when the cysts were tapped and reappeared as the cyst fluid again accumulated. In view of these considerations Rumpel and Reicher studied by means of the roentgen ray the effect which upward diaphragmatic pressure has upon the circulatory structures of the thorax and found that one of the most marked results was a diminution in the size of the retrosternal space. Since this space houses the large vessels of the heart, the authors postulate that these vessels, particularly the pulmonary artery, are brought during pregnancy into closer contact with the surrounding structures and will the more readily transmit the sound of coursing blood to adjacent tissues and thence to the chest wall.

Some plausibility is lent to this explanation if we consider the effect of posture upon the physiologic cardiac murmurs of pregnancy. In a study of 1329 women who were between seven and ten months pregnant, Walter Frey found that 203,

or 30 per cent, presented systolic murmurs when in the recumbent position; whereas only 85, or 12 per cent, showed murmurs when standing. Since he was also able to show by roentgen ray studies that the recumbent position decreased the size of the retrosternal space, he was inclined to associate heart murmurs heard in pregnancy with the diminution of the size of this space and so concurred in the view of Rumpel and Reicher. Aside from their scientific interest, these studies of Frey are of obvious practical importance since they point to the necessity of examining heart murmurs during pregnancy with the patient in the standing as well as in the recumbent posture.

The physiologic heart murmurs heard in pregnancy are rarely, if ever, diastolic in time. It is true that Gammeltoft in his series of 239 normal pregnant women reported diastolic murmurs in a few instances, but it is to be noted that these were heard only over the base of the heart and not over the mitral area. Walter Frey found 2 such cases among 207 women in the latter half of pregnancy. As a general rule, diastolic murmurs are not physiologic, but are evidence of rheumatic heart disease.

In Gammeltoft's study of 239 normal pregnant women, to which we have just referred, he found in 39, or 16.3 per cent, circulatory signs and symptoms of sufficient severity to suggest heart disease. Many of these patients, 24 of the 39, complained of dyspnea during the last months of pregnancy. The urine contained albumin in 19 instances. Edema was present in 34 cases. Physical examinations showed enlargement of the heart, murmurs, extrasystoles, accentuation of the pulmonary second sound, venous pulsations and rapid pulse. The chief complaints of these patients were cardiac pains and distress, headache, and shortness of breath. However, digitalis and rest in bed had no effect upon either the signs or symptoms of these women. When they went into labor, it was impossible, even by the most careful observation, to demonstrate any aggravation of the symptoms during the whole process and when they were discharged two weeks postpartum, practically all the abnormal findings had disappeared. Indeed, the murmurs were no longer audible on the day after delivery.

The report of Gammeltoft is in close accord with that of Hamilton of Boston, who finds that about 7.5 per cent of all

pregnant women coming to the antenatal clinic of the Boston Lying-in Hospital are referred to the cardiac clinic because of symptoms and signs suggestive of heart disturbance. Only about a third of these patients, however, have definite heart disease.

In view of all these difficulties and pitfalls *the conscientious obstetrician will usually hesitate to make a diagnosis of heart disease in a pregnant woman and will depend upon his cardiologic confrère to establish or rule out the existence of this complication.*

The second help which the obstetrician will expect from the cardiologist is in prognosis. Heart disease is a treacherous complication of pregnancy. While the majority of cases go through pregnancy, labor and the puerperium without incident, many follow courses which are difficult to foresee. Between 5 and 10 per cent of the mothers die before the puerperal state is ended.

The prognosis of heart disease in pregnancy resolves itself essentially into balancing the work which pregnancy, labor and the puerperium will impose upon the heart against the cardiac force available to carry out this work. The first of these factors, namely, the work imposed by pregnancy, labor and the puerperium, is of various kinds. In the first place, investigators are in general agreement that pregnancy is associated with a substantial increase in cardiac output, the average increment being about 50 per cent. This is, of course, what one would expect, since during gestation there is a large increase in the area of the circulatory bed due to the growth and vascularization of the uterus. Along with this, a proportionate increase in the total blood volume occurs, in order that the newly vascularized area may be filled. Accordingly, in pregnancy, there is a greater amount of tissue to be supplied with blood and more blood in the circulatory system to be pumped, adjustments which would naturally demand an increase in the minute output of the heart.

This increase in the cardiac output which occurs in pregnancy is a change of fundamental importance. It allows us to dispense with such vague phrases as "the strain of pregnancy" and permits us to speak in quantitative physical terms as follows: as the result of pregnancy the heart is obliged to per-

form on the average 50 per cent more work than it did in the pregravid state. The work involved in labor varies with certain obstetrical factors, notably parity, and if need be, can be reduced to a minimum by operative delivery, that is by low forceps delivery, or, if the cardiac reserve be very depleted, cesarean section. In estimating the work which pregnancy puts upon the heart, social conditions may exert a decisive influence. Thus, a well-to-do woman with a serious heart lesion may, with the help of servants, so minimize her activities during gestation that she will escape the toll which a working woman with a milder lesion would be forced to pay. Finally, the work imposed by pregnancy does not end with the puerperium, for the baby in the crib is sometimes a greater burden than the baby in the womb. The mother must expect for several years the interrupted sleep and the countless additional steps which every infant brings. This aspect of heart disease in pregnancy is seldom touched upon, but must be given due consideration if the problem is to be approached with far-reaching vision.

So much for the work involved in pregnancy and labor. Turning now to the other side of the balance, the cardiac forces available to carry out the work, this estimation is a more difficult one and falls to the cardiologist.

Naturally I do not feel competent to discuss those factors upon which the cardiologist will estimate the reserve forces of the heart but I should like to point out the desirability of the cardiologist and obstetrician using a *common language* when discussing this problem. I know of no better common language than the classification of the New York Heart Association, a classification based on the functional capacity of the heart.<sup>1</sup>

<sup>1</sup> New York Heart Association classification.

"Class I.—Patients with organic heart disease able to carry on ordinary physical activity without discomfort. Ordinary physical activity does not cause undue fatigue, palpitation, dyspnea or chest pain. Patients in this class do not show physical signs of congestive heart failure and rarely signs of active heart infection.

"Class II.—Patients with organic heart disease unable to carry on ordinary physical activity without discomfort.

"Class II A.—Activity slightly limited. Ordinary physical activity causes undue fatigue, palpitation, dyspnea or chest pain. Patients in this class rarely show physical signs of congestive heart failure or signs of active heart infection.



Pardee, as well as McIlroy and Rendel of London, have applied this classification to heart disease in pregnancy with eminent success. In actual practice, of course, the placing of these patients in the correct categories is not always simple. Border-line cases are common. While exercise tests facilitate classification, the results are sometimes invalidated by the nervousness of the patient and the strangeness of the movements involved. It is therefore necessary that the functional capacity of the heart be evaluated from as many viewpoints as possible, not forgetting the behavior of the heart in previous pregnancies and labors.

Of course, there are further questions which the obstetrician will wish to put to the cardiologist. For instance, he may wish advice concerning the desirability of prenatal digitalization as a prophylaxis against heart failure in labor and concerning the recognition of early signs of heart failure. However, as I have suggested, *the two principal facts which the obstetrician expects to learn from the cardiologist are: first, the diagnosis of rheumatic heart disease, and second, an estimation of the functional capacity of the heart.* These constitute the main responsibilities of the cardiologist. *To the obstetrician it now falls to adjust the work imposed by pregnancy and labor in such a manner that it can be easily accomplished by the cardiac forces at hand.* This adjusting of the work involved in pregnancy and labor in accordance with the functional capacity of the heart is the main responsibility of the obstetrician.

The manner in which the obstetrician carries out this task will, of course, vary greatly according to the needs of the particular case. With rare exceptions patients grouped in Class I and Class II A may be allowed to go through pregnancy and the first stage of labor; if the second stage promises to be short, spontaneous delivery may be permitted, but if it threatens to

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*"Class II B.—Activity greatly limited. Less than ordinary physical activity causes fatigue, palpitation, dyspnea or heart pain. Patients in this class usually show one or more physical signs of congestive heart failure, or the anginal syndrome or signs of active heart infection.*

*"Class III.—Patients with organic heart disease and with symptoms or signs of heart failure at rest, unable to carry on any physical activity without discomfort. There is fatigue, palpitation, dyspnea or chest pain at rest. Patients in this class show marked physical signs of congestive heart failure or the anginal syndrome, or signs of active heart infection."*

be long, delivery by forceps is usually desirable. The successful handling of these patients, however, necessitates punctilious prenatal care and constant supervision during labor. It resolves itself into four chief considerations: adequate rest during the whole prenatal period, avoidance of upper respiratory infections, recognition of early signs of heart failure and care during labor. A period of rest in bed in the hospital, preferably for a week or two, is always a beneficial preparation for parturition. With active labor begun, the patient should be placed and kept in a semirecumbent position with the head and shoulders well elevated by pillows. Observations on the pulse and respiration should be made every half hour during the first stage of labor and every ten minutes during the second. A rise in the pulse rate above 115 or in the respiration above 28, particularly when associated with dyspnea, are signs of cardiac embarrassment which, unless checked, may become forerunners of heart failure. Only in the presence of a completely dilated cervix, however, may they be taken as indications for delivery. With the cervix only partially dilated and the patient showing evidence of cardiac embarrassment, there is no known method of delivery which will not tend to precipitate rather than to forestall heart failure. Under these circumstances the treatment is always morphine and digitalis. If this treatment is not effective and the signs of cardiac embarrassment persist or become more marked, it simply means that a grave error in prognosis has been made. Such a patient should never have been allowed to go into labor. Her treatment, as well as her prognosis, is now that of heart failure in labor, a subject which will be discussed shortly.

Patients whose cardiac reserve is so diminished that they have been grouped in Class II B present difficult problems and the obstetrician must reduce to a minimum the work imposed on these patients. Rigorous rules for rest during the prenatal period must be laid down. It is indeed advisable that patients in this group spend one full twenty-four hours out of every week in bed. Should frank heart failure develop during the course of pregnancy it should be an absolute rule that the patient remain in bed in the hospital throughout the remainder of the pregnancy.

The method chosen for delivering patients in Class II B

will depend upon the history of the present pregnancy and the parity of the patient. If there has been no history of heart failure and if the patient is a multipara, delivery by the natural passages may be permissible. In the majority of patients in this group, however, cesarean section will be the procedure of choice. If decompensation has occurred during the present pregnancy, the operation should be done under local infiltration anesthesia. If no recent heart failure has occurred the noninhalation anesthetics are still to be preferred, but "open ether" is permissible. The operation should be performed with the head and shoulders slightly elevated. *Under no circumstances should a patient with heart disease be subjected to the Trendelenburg position.* At the close of the cesarean section the patient should be sterilized by a suitable operation on the fallopian tubes, provided, of course, that the written permission of husband and wife has been obtained.

But at the best, patients in Class II B face considerable risk in childbearing. If a woman in this group has already several living children and presents herself to the physician in the first trimester of pregnancy, it does not seem justifiable to ask her and her family to face this risk. In many such cases therapeutic abortion would seem to be the procedure of choice.

The treatment of patients in Class III resolves itself essentially into the treatment of heart failure in pregnancy, labor and the puerperium. A cardinal fact to be remembered in handling this type of patient is the following: *in the presence of heart failure delivery by any known method carries with it a maternal mortality of over 50 per cent.* Accordingly, the treatment of heart failure in the puerperal state becomes chiefly a medical one, the salient objective being to allay the decompensation. Only when this has been accomplished can one deliver the patient with a fair degree of safety. Occasionally, in patients whose heart failure resists therapy, one is forced to operate in the presence of varying degrees of decompensation, but, as we have already emphasized, delivery under these circumstances carries a grave prognosis. The method of choice for delivering patients in Class III is usually cesarean section under local infiltration anesthesia, but in multiparae spontaneous delivery in bed sometimes yields better results.

Should patients with heart failure start into labor, an

attempt should be made to stop parturition by means of liberal doses of morphine. Even when patients are well into the first stage of labor, it is frequently possible to halt uterine contractions for a sufficient period of time to restore a certain degree of compensation.

In dealing with cases of heart failure in pregnancy the argument is sometimes advanced that "the burden of pregnancy is too much for the heart" and that "removing the load of pregnancy will restore compensation." Were there some magic way of causing the pregnancy suddenly to disappear this might be true. But there is not. The only methods of delivery at our disposal inflict trauma, and when this trauma is superimposed on heart failure, it is enough to kill one half the mothers.

## CLINIC OF DR. HUGH HAMPTON YOUNG

THE JOHNS HOPKINS HOSPITAL

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### DIAGNOSIS AND THERAPEUTIC INDICATIONS OF VARIOUS DISEASES OF THE PROSTATE

THE prostate is so situated that many accurate methods of examination for differential diagnosis may be carried out with ease. Its proximity to the perineum makes it easily palpable by rectum, and its secretion may be obtained for microscopic examination. Its position around the urethra makes it possible to view the interior of the prostate and to note the condition of its constituent ducts with the urethroscope or cystoscope. Its relations to the bladder may be also studied in a similar way. By means of palpation upon instruments within the prostate, the thickness of certain portions may be accurately determined. With the *x*-ray accurate information can be obtained concerning many details of prostatic disease. The seminal vesicles, which must be included in every study of the prostate, also lie within easy reach and may be studied by similar methods. If it is necessary to see, feel and carry out biopsy upon the prostate, it is easily reached extraperitoneally through the perineum, or through the suprapubic region, and also by means of transurethral operations. There is hardly any organ in the body which can be so satisfactorily studied by so many methods as the prostate.

#### ANATOMICAL CONSIDERATIONS

The prostate is enveloped not only in its own capsule propria, but by two layers of fascia (Fig. 98) which effectively guard against the spread from the prostate to adjacent structures, not only of ordinary infections and tuberculosis, but also malignant disease, for a time at least. These layers of fascia

continue up posterior to the seminal vesicles and vasa deferentia, and thus determine the course in which disease spreads from the prostate. The distribution of the glands of the prostate are important in many ways. Immediately along each side of the urethra are a series of glands, which are the seat of early lateral hypertrophy. External to them is an entirely different group of glands which take little or no part in hypertrophy. Beneath the urethra, and separated from the lateral lobes by a fibrous layer, is the posterior lobe



Fig. 98.—Showing fasciae surrounding prostate, seminal vesicles and ampullae of the vasa deferentia.

or transverse lamella (Fig. 99) which also takes part very rarely in prostatic enlargement, but is by some strange fate the site in which carcinoma usually begins. The median portion of the prostate beneath the vesical neck and anterior part of the trigone is still another separate division which plays a very important part, particularly in obstructive diseases of the prostate. The relation of the bladder to the prostate is very important (Fig. 100). The trigone, as it converges to the vesical orifice, passes down over the median posterior part of the prostate, and is lost in the floor of the urethra. As we

have shown, the trigone plays the initial rôle in micturition. When stimulated by the desire to urinate, contraction of the

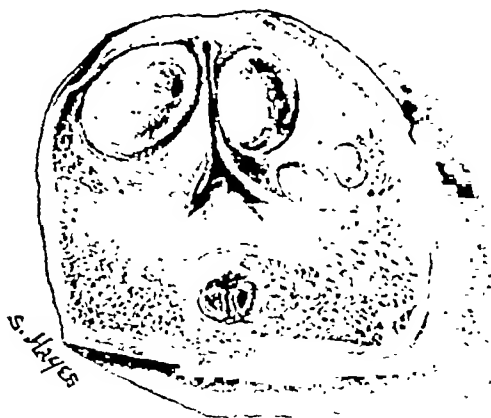


Fig. 99.—A cross section of an early hypertrophy of the prostate. In the lower portion are visible the ejaculatory ducts and the dilated orifices of some gland acini.

trigone pulls the posterior margin of the prostate downward and outward, thus opening a triangular aperture, through which

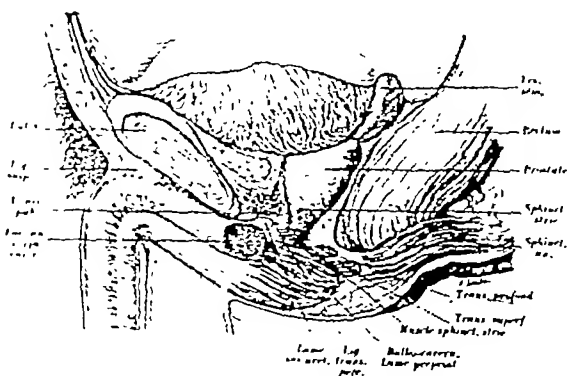


Fig. 100.—External view of the bladder, prostate, external sphincter muscles of the perineum and anus.

the detrusors force the urine during micturition. The closure of the prostate is accomplished by contraction of lateral muscles, which are easily seen endoscopically when the urethral orifice is opened, and particularly when they contract to draw

the uvula vesicae forward to close the orifice. In the floor of the urethra lies the crista galli, the verumontanum with the orifice of the utricle or vagina masculina, and on each side the orifices of the ejaculatory or wolffian ducts. In certain genital abnormalities the müllerian structures may form a definite vagina, which opens into the urethra at the site of the verumontanum, or in females the müllerian tubercle. In female pseudohermaphrodites, not infrequently, the hymen is found in the floor of the urethra surrounding the opening of the vagina into the urethra or at its junction with the urogenital sinus below. Various abnormalities of the wolffian and müllerian systems lead to complex pictures of great interest. The sphincters are also closely related to the prostate: the internal, we have already described; the external surrounds the apex of the prostate and the membranous urethra. The sphincter medius is an indefinite muscular structure between the two. These sphincters, as we show later, play an important part in the escape of secretion and inflammatory products from the prostate.

#### METHODS OF EXAMINATION

The urinalysis will often give an indication of the condition of the prostate. For this purpose the three-glass test is used. Any secretion from the prostate, which has escaped into the posterior urethra, will be washed out in the first urine passed and found in the first glass. The second urine, passing through a clean prostatic urethra, may be clear and negative, while the third glass, which represents the last urine expelled from the bladder and deep urethra in the final spasmodic act of micturition often contains secretion or shreds from the prostatic or ejaculatory ducts. Secretion, purulent exudates and bacteria in the anterior urethra may also be found in the first urine voided. By cleansing the anterior urethra—that portion which lies between the meatus and the external sphincter—with irrigations or injections of sterile water, one may obtain in the first glass urine uncontaminated by the anterior urethra. It is thus possible to remove the smegma bacillus, which is practically never found in the prostatic urethra. Any acid-fast organisms obtained, especially in the last urine voided after the anterior urethra has been examined, may be recognized as tubercle bacilli. The failure to obtain urine in three separate



glasses has led to many mistakes in diagnosis. By this simple means it is possible to show that the urine which comes from the bladder and kidneys is clear and that the pus found in the first urine voided comes from the urethra, either posterior or anterior.

**Rectal Examination.**—After the urine has been voided in three glasses, as above described, the next procedure is usually to examine the prostate with the gloved finger introduced through the anal sphincter. One should note the condition of the sphincter, whether of normal tone or pathologically relaxed. The condition of the rectal wall—smooth or rough, movable, adherent, infiltrated or ulcerated—should be noted.

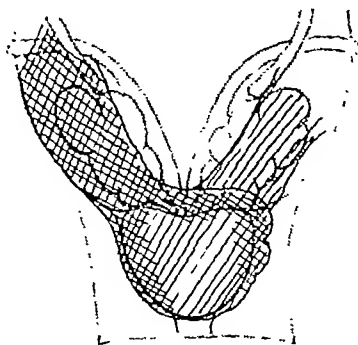


Fig. 101.—Case of marked prostatitis and seminal vesiculitis. First degree induration indicated by parallel lines in one direction. Second degree induration indicated by cross lines. Prostate and seminal vesicles are both enlarged. (BUI 8486.)

The prostate, which lies immediately beneath the rectal wall, should be studied by the palpating finger and the results carefully charted. It is usual first to examine the median notch and furrow, then in sequence the left and right lateral lobes, the borders of the prostate, their relations to the external sphincter, triangular ligament and Cowper's glands, the relation between the seminal vesicles, ampullae, the prostate and the structures which surround them.

As shown in Figs. 101 and 102, these findings are recorded on a chart. In Fig. 101 the prostate was irregular, slightly enlarged in places and with induration of first and second degree. One seminal vesicle was enlarged, indurated, second

degree, and the other, first degree. In Fig. 102 is shown a prostate with an oval area of induration of third degree. This isolated enlargement led to the suspicion of either carcinoma or calculus. The latter was ruled out by an x-ray which showed no shadows. These graphic charts should generally be employed, because they give at a glance the findings of the examining finger and contribute materially to the accuracy of the examination and the records.

*x-Ray.*—The x-ray is of great value and, in the simple film, may often show areas of induration indicative of calculus. These pictures should always be taken with the rays directed down the strait of the pelvis, so as to show the prostate unobscured by the symphysis pubis. By dropping the legs of

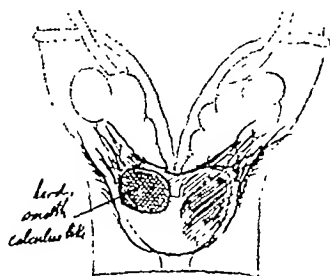


Fig. 102.—Chart of rectal examination; clinical diagnosis, carcinoma. Radical operation: April, 1914. Pathologic report: carcinoma. Letter (October, 1936): "Well. Urination normal." (Twenty-two years since operation.) (BUI 3913.)

the patient over the end of the table and placing a pillow beneath the small of the back, no difficulty is experienced in so placing the x-ray tube that rays will travel directly down the pelvic strait and show the prostate within the shadow of the pelvic girdle. Shadowgraphic pictures of the prostatic urethra may be obtained by injecting various substances into it. Stereoscopic films add greatly to the value of these x-ray studies of the prostate. The utricle and ejaculatory ducts may easily be injected with shadowgraphic material through a urethroscope and x-ray films may then demonstrate various abnormalities of the structures above the prostate, as will be discussed later. Pockets, cavities, diverticula and other abnormalities may also be disclosed in a similar way.

The subjects to be considered in this brief paper may be tabulated thus:

1. Abnormalities.
2. Injuries.
3. Inflammations.
4. Calculi.
5. Obstructions, including tumors.

A further classification under these headings will be given along with the differential diagnosis and therapeutic indications, as prescribed.

#### ABNORMALITIES OF THE PROSTATE

The development of the prostate depends greatly upon endocrine influence. In this the testicles, the hypophysis and probably also the structures in and about the third ventricle, as well as the thyroid and adrenal, play important rôles.

**Hypogonadism.**—Hypogonadism is usually accompanied by a failure of the prostate to develop normally; in fact, it is often so small as to be practically impossible to palpate with the rectal finger. In these cases the testicles, and often the penis, are small and undeveloped, and the patient has marked changes in the secondary sex characters: lack of beard and hair in other parts of the body accompanied by unusual deposits of fat, so as to give the patient a feminine figure, often accompanied by an increase in the size of the breasts, amounting at times to definite gynecomastia. More pronounced cases are generally thought to be due to changes in the pituitary and are diagnosed dystrophia adiposogenitalis. Generally, the differential diagnosis is evident. The minute differentiations, according to the different endocrine glands, which are responsible for the condition, are complex and wrapped in much obscurity.

**Therapy.**—Unless some gross pathological condition, such as tumor of the testicle, of the adrenals, pathological conditions of other endocrine glands can be found, one must depend on hormone treatment. In the present state of our knowledge, which has been so rapidly added to in recent years, it is impossible to state definitely just what glandular extracts or synthetic compounds are of most value. We have collected elsewhere<sup>1</sup> a study of hypogonadism and the changes in the

prostate which accompany it. Marked benefit has been described by some authors, but many others have had no results with endocrine therapy.

Testicular implantation has been successful in some instances, but here again we must wait for much more laboratory and surgical experience before definite progress can be reported.

**Irregular Development of the Prostate.**—This abnormality may assume various types: the absence of one or more lobes and their constituent ducts, etc. The diagnosis of these may be made by rectal and instrumental examination, but these conditions are rare, and usually found at autopsy.

The most important of the abnormalities are congenital obstructions either at the prostatovesical orifice, generally known as the vesical neck, or along the course of the prostatic urethra.

**Congenital Obstruction at the Vesical Neck.**—The differential diagnosis of these conditions depends upon the history of difficulty and frequency of urination, generally evidenced at birth, or coming on in childhood. With the advent of infection and other complications the symptoms may greatly change, infection, pyuria, irritation, pain, complete retention of urine, back pressure effects upon the ureters and kidneys, systemic effects, such as gradual onset of uremia, pyrexia, etc., all are conditions which must be considered in differential diagnosis. This is finally made by instrumental studies, which disclose the presence of obstruction at the vesical neck, visual inspection by means of the cystoscope demonstrating a bar, valve or lobule at the vesical orifice or a contracture surrounding it, the presence of residual urine, hypertrophied trigone, trabeculated and cellular bladder, impaired renal function and blood studies. These conditions must be differentiated, especially in children, from congenital valves, usually springing from the verumontanum in boys, diaphragms across the urethra lower down, hypertrophy of the verumontanum, and prostatic cysts. By means of instruments, cystoscopy, urethrograms and cystograms, the differential diagnosis can usually be made.

**Therapy.**—This is entirely surgical. The removal of the obstructing condition can usually be accompanied by trans-

urethral operations, the technic of which may either be that of the punch operation, in which the obstructing condition at the vesical orifice is caught in a fenestra, excised with an inner cutting tube, either sharp or electric. Persistent bleeding may be easily stopped by electrocoagulation, preferably with a single electrode point. The technic of these procedures is given in the surgical literature.<sup>2</sup>

**Congenital Valves.**—Those which are found in boys usually spring from the region of the verumontanum, and extend as thin folds of mucous membrane, or diaphragms, out to the urethra on each side, leaving a small aperture either circular or slitlike between the folds of mucous membrane. Congenital valves manifest themselves usually at birth, and are often accompanied by very severe uremic symptoms, associated with great dilatation of the upper urinary passages, and marked destruction of the renal cortex. In these cases a marasmic child, with distended abdomen, generally has a palpably enlarged bladder, and in many instances the kidneys and ureters can also both be palpated, and even seen through the thin abdominal wall. The urine is voided with great difficulty, and frequency, sometimes in driblets. Occasionally incontinence is present. An instrument passed into the urethra usually meets with complete obstruction about the middle of the prostatic urethra. Often every type of catheter or bougie is arrested. With the passage of a small urethroscope, one may generally see the aperture between the diaphragmatic folds and make a visual diagnosis. Sometimes a filiform can by manipulation be forced into the bladder, and the obstruction greatly dilated by followers. A cystoscope may then be introduced, and the valve seen, the dilated prostatic urethra above made out along with the trabeculated cellular bladder, and dilated ureteral orifices. If instrumental examination fails, a cysto-urethrogram may often furnish the diagnosis by demonstrating the dilated urethra above the valves, and regurgitation into the greatly enlarged ureters and renal pelves (Fig. 103). Intravenous urograms are also of great value, and show the characteristic lesions in the upper and lower urinary tract. Here again the differentiation must be made from obstructions in the outer part of the urethra, as cited above.

**Therapy.**—This is surgical. Complete removal of the val-

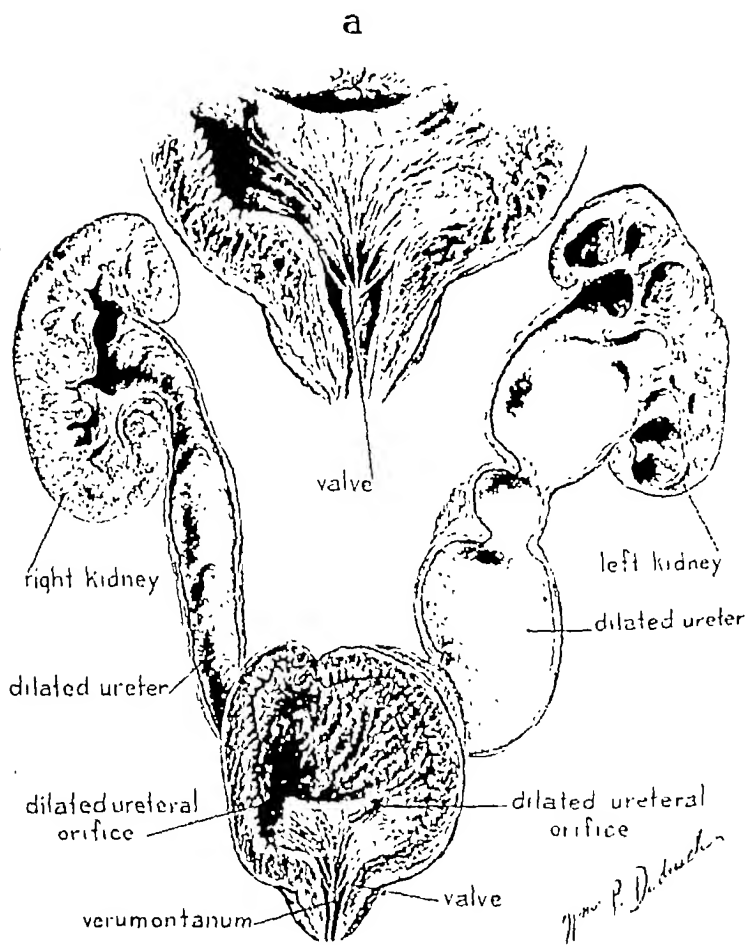


Fig. 103.—Autopsy specimen. Patient entered hospital in extremis. Showing congenital valves of posterior urethra, type 2. Note the dilated ureteral orifices, hydro-ureters with partial destruction of kidneys *a*, Showing enlarged view of posterior urethra and valve formation. The valves originate at the proximal end of the verumontanum, and are attached laterally to the side and anteriorly to the roof of the prostatic urethra. Note great dilatation of vesical orifice. (BUI 13248.)

vular obstruction is necessary. Sometimes this can be accomplished by the simple passage of instruments. After a filiform has been successfully introduced, large dilators may be safely passed. Without such a conductor, any attempt to pass

progressively larger sounds may be fraught with danger, as false passages have been reported with fatal ending. The use of Young's baby punch to grasp and remove the valves has been employed in many cases, especially at our clinic. Endoscopic fulguration of the valves has also been successful in many cases. We have recently collected a series of 32 cases from our clinic, and have given in detail the therapy used, and our results.<sup>1</sup> This report is accompanied by a study of the literature, which shows that whereas the condition has been known to exist for over a century, it was not until 1912, when we recognized the condition clinically and carried out an operation to relieve it, that the surgical therapy was put on a firm basis.

**Cyst of the Prostate and Its Adnexa.**—This condition furnishes interesting problems in differential diagnosis. These cysts may arise from almost any portion of the prostate, and sometimes cause marked obstruction and even complete retention. Those at the prostatic orifice may simulate lateral, median or anterior lobes. They are usually recognized by their translucency on cystoscopic examination. This is confirmed by applying a coagulating electrode, which will promptly lead to evacuation of a cyst. Aspiration has sometimes been carried out as a diagnostic procedure. The use of a cystoscopic rongeur may be helpful in diagnosis. In those cysts, which spring from the ducts in the verumontanum, shadowgraphic demonstration with the x-ray, after injecting the utricle and ejaculatory ducts, may furnish immediate diagnosis. In some of these cases the cystoscope will show an elevation of the trigone, which confirms the rounded, elastic, often fluctuant mass made out on rectal examination, generally above the prostate in the region of one of the vesicles, or between the two. When the cyst remains within the capsule of the prostate, the differential diagnosis between cyst and abscess may be difficult. If there is an orifice connecting it with the urethra, the cyst may assume the characteristics of a diverticulum, and be readily demonstrable by simple urethrogram. It may also be seen, probed or catheterized with an endoscope. By the methods above mentioned, the differential diagnosis is usually made without difficulty and the therapeutic indications readily surmised.

**Obstructive Cysts at the Vesical Orifice.**—These may be readily attacked by endoscopic and transurethral methods, as above outlined. Those of the genital ducts may be given satisfactory drainage by enlargement of the strictured utricle or ejaculatory ducts. In cases in which they cannot be reached and evacuated in this way, perineal excision may be readily carried out without entering the urinary tract.

**Congenital Enlargement of the Verumontanum.**—This is a rare condition, but may produce the typical symptoms of prostatic obstruction. A case, which has been successfully operated on, has just been described by us.<sup>1</sup> The symptomatology and cystoscopic picture may closely simulate that of a median lobe or prostatic obstruction, but the urethrogram, showing dilatation of the prostatic orifice above the enlarged verumontanum, and urethroscopy indicating that the globular mass extends down to and occupies the place of the verumontanum, make the differential diagnosis clear.

The *therapy* in these cases is surgical, and consists in transurethral resections or removal through a cystotomy, but the latter should seldom be resorted to.

**Sexual Abnormalities.**—These may best be considered here. The abnormalities are generally in physiologic functioning of the prostate and its adnexa during coitus. The most common condition is that of premature ejaculation, often caused by an enlargement, hyperemia and hypersensitiveness of the colliculus. In some cases strictures of the ejaculatory ducts, and even of the orifice of the utricle, may be important contributory factors, all of which may be recognized by the endoscopic and radiographic methods referred to above. In other cases the sexual abnormality is more extensive, involves the libido of the patient, his ability to have erections, and to consummate intercourse. These conditions are often complicated by inflammatory conditions, which must be referred to further on.

The nervous system plays a very important part, and sexual neuroses are among the most common of ailments. Not infrequently a study of these cases involves the domain of psychiatry. The differential diagnosis is clear; the treatment often complex. Much can be accomplished by local measures, such as stimulating massage through the rectum applied to the



vasa deferentia, seminal vesicles, ejaculatory ducts and lateral lobes of the prostate. This treatment should not be overdone, and should usually be gradually lessened and confined to the region of the ejaculatory ducts and verumontanum, so as to avoid removal of the fluids collected in the vesicles and ampullae, which themselves act as powerful stimulants to libido and erections. Treatment through the urethroscope, with dilators, nitrate of silver or milder antiseptics, and stimulating drugs, are of great value, but one must guard against overdoing, and combine the treatment with psychotherapy, which means getting the confidence of the patient, persuading him that his condition is not serious, that there are definite but slight pathologic conditions, which are the cause of his abnormal sexual condition, but which can eventually be removed by these simple means. If the patient can be made to cease his worrying, have confidence in the curability of his case, and be persuaded not to attempt intercourse until the libido has returned, he can often be extricated from this deplorable mental and physical condition.

### INJURIES

Injuries of the prostate are usually caused by an attending physician or nurse who, in passing sounds, catheters, cystoscopes, or other instruments, traumatize the urethra and occasionally produce false passages of greater or lesser extent and gravity. At operations upon the prostate, either transurethral, suprapubic or perineal, grave injury may result from mistaken technic. I have seen a case in which a perineal operation, by breaking through the anterior capsule of the prostate, gave entrance to infection of the prevesical space, with fatal ending. Such conditions have also followed transurethral resections and suprapubic operations. Injury of the prostate from external traumatism is rare. The solidity and strength of the prostate and surrounding capsule are sufficient to protect it. Urethral ruptures are usually at the apex of the prostate, which not infrequently is entirely severed and completely separated from the membranous urethra. It is hardly necessary to dwell upon the differential diagnosis of these conditions, which usually become self-evident after the

occurrence of the traumatism. The therapy depends upon the condition and the complications present.

### INFLAMMATIONS

**The Gonococcus.**—Gonococcus infection of the prostate has been common in the past. It has been variously estimated that in between 50 and 75 per cent of all cases of gonorrhea the prostate becomes involved. Not infrequently only the posterior urethra or ducts immediately surrounding it are invaded, and the symptoms may be so slight as to make the differential diagnosis difficult. If the secretion is only sufficient to fill the posterior urethra, and therefore does not flow back into the bladder, when the urine is voided pus from the prostatic urethra will be washed out by the first urine voided and appear only in the first glass, unless the prostatic ducts be sufficiently involved so that, in the final spasm of emptying the urine from the bladder and prostatic urethra, purulent secretion from the ducts is forced out and appears in the third glass. When the secretion is more abundant, after filling the prostatic urethra, it flows back through the internal sphincter into the bladder, and all three glasses contain cloudy urine. If the involvement of the prostate is more extensive, local pain, especially on urination, may occur, and in rare cases, this may be so severe as to produce strangury. If the swelling within the prostate becomes markedly increased, difficulty of urination, with gradually increased frequency and finally complete retention of urine (in rare cases), may occur. In such cases the diagnosis between obstructive conditions due to *other* causes must be considered. On rectal examination the prostate may show little change when the involvement is slight, but in other cases it may show definite enlargement, softening and even fluctuation when the inflammation tends to be localized. The seminal vesicles and ampullae are apt to become involved by the gonococcus, and here again the symptoms and findings vary according to the severity and extent of the inflammatory lesion. The examining finger detects changes in these structures, and indicates the progress of the disease. In acute gonococcus infections of the urethra, instrumentation is to be avoided at all cost, if possible, so that even in marked difficulty and frequency with definite evidence of obstruction,

catheterization is usually not to be done. By careful palpation and percussion of the bladder, the presence of considerable residual urine can usually be made out, and urography may also be employed to assist in the determination of prostatic obstruction. When there is fear of involvement of the kidneys, either as a result of back pressure, or by ascending infection, blood chemistry may be of diagnostic value. As the disease becomes subacute or chronic, the more rigorous diagnostic methods may be employed, including massage of the seminal vesicles and prostate, with bacteriologic study of the expressed secretion, instrumentation of the urethra, including endoscopy, cystoscopy, and sometimes probing of the ducts in the verumontanum. In acute, subacute and chronic gonorrheal prostatitis, the use of the prostatic chart is of great clinical value. As shown in Fig. 102, the areas of irregularity and induration are shown as well as adhesions and involvement of adjacent structures. Of considerable diagnostic value are referred pains in the back, hips, thighs, legs and groin, which often may be the only symptom accompanying chronic prostatitis and vesiculitis. The frequent presence of symptoms quite remote from the prostate shows the great importance of routine rectal examinations, with charting of the prostate and its adnexa, study of the secretions, microscopically and bacteriologically. These are simple procedures which may be carried out by any practitioner, and often clear up a puzzling case. When the disease is associated with sexual symptoms and neuroses, urethroscopic study of the posterior urethra and its ducts may be of great diagnostic value in these cases of chronic prostatitis. The differential diagnosis between infections of the prostate by the gonococcus and other organisms is not always easy; in fact, the common bacteria as well as tubercle bacilli may occasionally bring on acute inflammatory conditions of the prostate and its adnexa which simulate closely those of acute gonococcal infection. The differential diagnosis will depend upon the microscopic and bacteriologic study of the case as well as the other measures referred to above.

*Therapy.*—When the gonococcus invades the posterior urethra, the clinical picture is often changed at once, and in addition to the usual methods of treatment, measures directed to allay the inflammatory condition of the prostate should be

undertaken. Rest in bed, application of heat to the perineum, and through a 2-way rectal tube to the posterior surface of the prostate and vesicles have long been employed. Should very severe obstructive symptoms occur, suprapubic aspiration of the bladder can often be carried out effectively. In most cases it may not have to be repeated more than two or three times, and using a fairly small needle, no danger is incurred. A case is reported in which the bladder was aspirated successfully more than one hundred times. After one or more aspirations, as a rule, the prostatic swelling and obstruction will diminish so that natural voiding returns.

We have employed very successfully intravenous therapy. One per cent mercurochrome in doses of 12 cc. of a 1 per cent solution injected into the vein is often effective in both acute and chronic gonorrheal infections of the prostate. In a previous report<sup>3</sup> we have detailed a considerable series of cases effectively treated in this way. In the several years that have intervened since that report, we have continued to employ chemotherapy particularly in deep-seated infections of the gonococcus. Starting with 12 cc. of a 1 per cent solution, in two or three days, one may give 14 cc. of mercurochrome with impunity, and again three days later, 16 cc., and four days later, 18 cc. Five days later one may give 20 cc. It is rarely necessary to exceed 18 or 20 cc. for a single intravenous injection of mercurochrome. One of course is guided by the reaction, and the interval may be prolonged if the diarrhea is pronounced, or the patient shows symptoms of pytalism. Febrile reaction, more or less pronounced, is to be expected, and is probably an evidence of the antibody reaction by which we believe the benefit is obtained. We have in our records a considerable series of cases in which gonococci, present for a number of years, have disappeared within one or two weeks of treatment with intravenous therapy.

A further extension of chemotherapy to the treatment of gonorrhea has recently been introduced by Dees and Colston.<sup>4</sup> In their first report they recounted the striking results which had been obtained by sulfanilamide given by mouth. In a further report<sup>5</sup> they cited some 40 cases in which the remarkable effectiveness of this new form of therapy was substantiated. The most striking feature was that the posterior

urethra rarely became involved. If future experience, with a great series of cases, confirms the results already reported, it seems probable that gonococcus invasion of the prostate may be greatly minimized.

In the treatment of gonococcus infections of the prostate, both acute and chronic, we have found it desirable to give urethral injections so as to reach the organisms which lie within the canal and are not reached through the blood stream. It may be found that this should also be employed when sulfanilamide is used. Denny has demonstrated to his satisfaction that his results are superior when such is done in conjunction with the oral therapy. Both intravenous and oral chemotherapy in the treatment of gonococcus infections of the urethra, and particularly the prostate, are still in their infancy, but we feel tremendously encouraged and confidently expect that great progress will be made in combating this great scourge to humanity.

**Prostatic Infections due to Other Bacteria.**—As stated above, the symptomatology and diagnosis in many cases of acute and chronic inflammations of the prostate may be almost indistinguishable clinically from those due to the gonococci. These may be just as acute and associated with as great local, remote and urinary symptoms. When the infection is engrafted upon a previously obstructing prostate, either of the congenital or the hypertrophied types, the symptoms may be greatly exaggerated. Chills, fever and other evidences of sepsis may be present, and extension to adjacent organs may occur, rendering hospitalization and operative intervention necessary. If the process goes on to abscess formation, rupture spontaneously into the urethra or bladder may alleviate the condition, but in other cases operative intervention may be required. The therapy in prostatitis due to ordinary bacteria, as remarked above, varies greatly with the organism, the extent of involvement, the symptoms and particularly the obstructive and painful conditions that may ensue. In acute cases the methods suggested in gonorrheal involvement may be equally applicable. With the recent advent of remarkable methods of combating infections of the urinary tract and even the deep-seated urinary organs, much has been accomplished by simple means. The introduction of hexamethylamine was a great advance.

In coccus infections, our use of neosalvarsan intravenously has often been effective in sterilizing infections, not only of the urine, but of deep-seated invasions of the prostate and other organs. Ketogenic diet, along with acidification of the urine, has often accomplished wonders in sterilizing the urinary tract of infections by the colon bacillus group. Intravenous mercurochrome has been ineffective in this group, and like neosalvarsan has occasionally been very efficacious in staphylococcus and streptococcus infections. The recent introduction of sulfanilamide bids fair to revolutionize the treatment, not only of coccus infections, but also of certain bacterial infections of the urinary tract and adjacent organs. We have recently seen a case of long-standing infection of the prostate, with multiple stones present, in which complete sterilization was obtained by sulfanilamide by mouth. The infecting organism was a *Staphylococcus aureus*. *Proteus* is reported by Helmholz to be eradicable with sulfanilamide. Others have reported that it has, in some cases, also proved effective for the colon group. The whole subject is new, and much additional work must be done, but there is evidence that by means of these new methods of chemotherapy, much can now be accomplished, not only in sterilizing the urine in simple bacteriurias, but also in eradicating the organisms from the deeper glandular tissues.

When prostatitis is superimposed upon obstructive conditions it is now generally recognized that closed operations, such as transurethral resections, are rendered more dangerous, and that open surgery, especially attack through the perineum, by means of which the infection may be adequately dealt with and drainage secured, is preferable.

**Infections of the Prostate with the Tubercle Bacillus.**—Although Guyon recognized many years ago the great frequency with which the prostate was involved in urogenital tuberculosis, and was often the initial site of the infection, the profession has been slow to realize the great importance of tuberculous prostatitis and seminal vesiculitis. Surgeons have been content to remove the external evidence of the urogenital infection in the epididymis, or to content themselves with nephrectomy, when the initial lesion was in the seminal tract. In a series of papers we have verified the accuracy of Guyon's

dicta, and have urged the profession to search for tuberculous lesions in the prostate and seminal vesicles, even though there are no localizing symptoms. Walker, and the recent paper of Moore, have verified the accuracy of our conclusions. The diagnosis of tuberculous invasion of the prostate and vesicles is often difficult. The lesion may long be inoffensive and simulate on rectal examination the findings present in chronic prostatitis and seminal vesiculitis. The finding of the tubercle bacillus, after carefully excluding the smegma bacillus by the methods mentioned above, will often furnish the diagnosis. The presence of epididymitis, especially when there has been no recent attack of gonorrhea or prostatovesiculitis due to common organisms should put one on his guard. In such cases careful examination of the prostate and vesicles is essential. The discovery of induration, nodules, adhesions, enlargement not associated with prostatic hypertrophy or contractures at the vesical neck, even if the tubercle bacillus is not found in the urine or secretions, may render the differential diagnosis positive. In this one must consider prostatic calculi, especially if associated with inflammatory conditions. The x-ray will usually, by its shadows of the stones, make the diagnosis clear. Carcinoma of the prostate must always be considered and in elderly men the differential diagnosis between tuberculosis and cancer may be extremely difficult. In cancer the lesion begins in one area in the prostate and gradually spreads, whereas in tuberculosis it is often multiple in its areas of involvement, the vesicles often being the primary seat. In case of doubt, one may well expose the prostate through the perineum, as early operative removal of both tuberculous and malignant disease is generally indicated. In late cases, study of the urethra with the x-ray may demonstrate tuberculous pockets, which open into the urethra. The cystoscope and urethroscope may also reveal much of value. Study of the upper urinary passages is indicated in many cases, as it is important to determine whether a tuberculous lesion is present in one or both kidneys.

*Therapy.*—This is entirely surgical. We have proved, to our satisfaction, that in tuberculosis of the seminal tract removal of the vesicles and lateral lobes of the prostate is indicated in a large majority of the cases, with total extirpation of the vas deferens and one or both epididymes, if these are

involved. In almost one third of our cases we have discovered one kidney involved, and have removed it in addition to the radical extirpation of the seminal tract. The results obtained by these extensive surgical procedures have been very gratifying, and, in our opinion, have shown that half-way measures fail to cure the patient and are followed by an extension to other organs of the urinary tract. It is well established that renal tuberculosis should be treated by nephrectomy and partial ureterectomy as soon as a diagnosis is made; we believe equally radical measures should be applied to tuberculosis of the seminal tract, and that in addition to removal of an involved epididymis and vas, in most cases the involved seminal vesicles and prostate should be attacked through the perineum. Our recent statistics fully justify this statement.<sup>6</sup>

#### CALCULI

The diagnosis of prostatic calculi is often difficult, due to the fact that no symptoms may be produced. In the endogenous form many calculi, varying in size from a millet seed to several millimeters, are usually scattered throughout the glandular tissues of the prostate. The symptoms may be those of simple chronic prostatitis. Rarely does one encounter much pain in these cases. With the onset of infection, more pronounced changes in the prostatic gland—adhesions to adjacent structures, involvement of the vasa and seminal vesicles, extension to the epididymes, sepsis, toxemia, febrile reactions and referred pains to other parts of the body—not infrequently supervene. Sexual disturbances may also occur. When these endogenous calculi ulcerate into the urethra, or approach closer to it through dilatation of the prostatic duct in which they lie, urethral symptoms, irritation, hematuria, pain on urination and ejaculation may come on. When such a stone escapes into the prostatic urethra, definite obstructive symptoms may occur, and if it slips into the bladder, it may gradually assume proportions sufficient to give the symptoms of vesical calculus. Pain referred down the urethra and into the glans is not infrequently present in prostatic calculi, which are still in the prostatic urethra, but more frequently when they have escaped into the bladder. In a recent report of 100 cases<sup>7</sup> of prostatic calculi we found that 50 were associated with prostatitis, 29



with benign adenomata of the prostate, 6 with prostatic abscess, 2 with carcinoma, 1 was entrapped in the prostatic utricle, and 7 showed no evidence of prostatitis. In many of these cases no symptoms were produced, and the stones were discovered accidentally. In some cases symptoms of chronic prostatitis, both local and referred, were present and in fact the patient was often treated for a long time for prostatitis. In these cases on rectal examination the prostatic findings were those of a simple chronic prostatitis. The stones were not palpable, no crepitus was elicited, and in fact no areas of

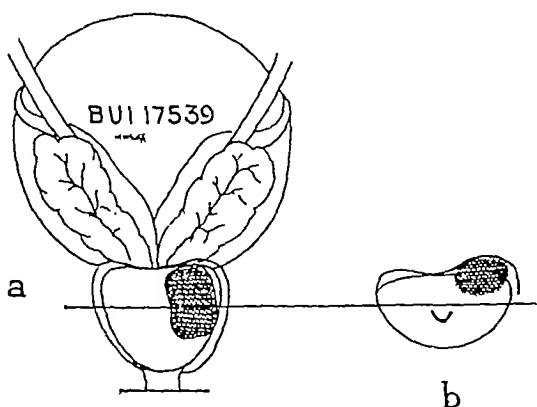


Fig. 104.—Rectal chart showing large area of calculi in right lobe of prostate in patient, aged forty-six years, with history of gonorrhea twenty-one years previously, and nocturia every two hours. The calculi were not detected by cystoscope. Removal of calculi by perineal prostatectomy. Removal of small bar, but not of lateral lobes. Result: excellent. (Young in Cabot's *Modern Urology*, Lea and Febiger, Publishers.)

marked induration indicated their presence. In one case, in which the patient had been subjected to massage and local treatment for many months, an *x*-ray showed calculi in great numbers in the prostate. It seems evident therefore that it would be a good plan to take adequate *x*-rays of the pelvis in order to rule out the presence of calculi in all cases of supposed simple prostatitis. As mentioned before, these *x*-rays should be taken so that the rays are directed down the pelvic strait in order to show the shadow of the prostate well within the pelvic girdle. Shadows in that region must be differentiated from phleboliths and also from calculi in the seminal vesicles,

vasa deferentia and in the bladder itself. Calcification of Cowper's glands must also be excluded. Rectal palpation will usually assist in these differentiations by an easy recognition of the location of the indurated area (Fig. 104).

*Therapy.*—This will depend largely upon the symptoms, both local and remote. In the presence of irritating, painful and sexual symptoms, which disturb the patient greatly, eradication of the stones either by urethral instrumentation, which may sometimes be successful, or perineal operation, which is more thorough and logical, should be employed. The presence of infection adds an additional reason for proper drainage, but we have recited above a recent case in which a staphylococcus infection of the prostate, in which many stones were demonstrated by the *x*-ray, was completely eradicated by the oral administration of sulfanilamide. If chemotherapy proves to be equally successful in the future, the operative removal of nonobstructive calculi, which cause little or no symptomatology, may be discontinued.

When the calculi are associated with prostatic hypertrophy, which is fairly common, the extirpation of the stones along with the prostatic lobes by enucleation through the perineum would seem to be the method of choice. The suprapubic region has never proved effective in removing calculi in such cases, as the calculi are usually situated in the tissues between the hypertrophied lobes and the encapsulating prostatic tissue, and therefore not reached or often removed in the suprapubic operation. As one passes through the region in which these stones lie, when attacking the hypertrophied prostate through the perineum, excellent opportunity is afforded for their complete removal. When the stones have been extruded into the urethra, removal by urethrosopic or cystoscopic instruments is often easy. When they slip out into the bladder they may be crushed and evacuated.

#### OBSTRUCTION

**Purely Vesical Neck Obstruction; Contractures, Bars and Small Lobes.**—In many of these cases the disease has been present since childhood. The patients have often noticed hesitation, difficulty and frequency of urination, have not been able to complete micturition with the speed of their associates.

Compensatory hypertrophy of the trigone and the bladder muscles may for a long time provide fairly satisfactory urination, but eventually the symptoms of obstruction and irritation, and in many cases back pressure effects, are such as to lead the patient to seek relief. In these cases the prostate may often feel almost normal by rectum. There is usually some induration, particularly across the upper portion, and in the region of the median notch and furrow. Prostatitis may be present and evident in the secretion obtained by massage. Cystoscopic study showing the presence of a contracture of the vesical orifice, a bar in the median portion, or elevated lobule which obscures a portion of the trigone, which itself is usually hypertrophied and accompanied by trabeculation of the bladder, makes the diagnosis easy. With an instrument in the urethra and a finger in the rectum, the increased thickness of the median portion, and generally presence of a firm collar at the vesical neck confirm the diagnosis. Further study of the case should include the clinical and laboratory studies, which are recognized as essential in the study of prostatic obstructions generally, particularly phthalein tests and blood chemistry.

Although many operative methods were employed years ago for conditions of this type, particularly by Mercier, it was not until Bottini brought out his electrical cautery incisor that complete transurethral removal with comparative safety of these obstructions at the vesical neck was accomplished. Chetwood, with his perineal cautery prostatotomy, reported numerous successful cases. In 1909 we introduced our urethrosopic median bar excisor or punch, provided with a fenestra which entrapped the obstructing portions of the prostate, and an inner cutting tube which excised it. With this simple instrument we reported in consecutive papers hundreds of cases in which these obstructions were removed with ease and freedom from danger.<sup>8</sup> The bleeding, which occasionally was active, was found to be arrestable by cystoscopic fulguration, the electrode being applied directly to the bleeding point, and thus avoiding deep and widespread destruction of tissue. The fenestrated punch has been variously modified in instruments introduced by Braasch, Bumpus and Thompson, all of whom employed our cold cutting punch. In 1911 we had already constructed an inner cutting tube bearing an electrocautery ring, with

which the entrapped prostatic mass could be excised without hemorrhage, we hoped. As time went on we found that the use of the simple cold cutting punch and fulguration of the individual points of bleeding was more satisfactory. This method has been employed in the Braasch-Bumpus-Thompson modifications of the punch. Caulk in 1921 modified and simplified the electric cautery punch, and has been a strong advocate of its use not only in contractures, bars and lobes at the vesical orifice, but for lateral enlargements as well. To Caulk is due credit for the introduction of transurethral surgery to the universal attack upon the obstructing prostate, regardless of its size. Stern modified the fenestrated punch by introducing a cutting loop, electrified by the high frequency current, and initiated the widely used method of transurethral, high frequency, electric resection of the prostate. A further modification of McCarthy and numerous other publications have led to the great popularization of transurethral resection of the prostate which will be discussed further on.

All these procedures may be employed satisfactorily for the subject under discussion: *contractures, bars and lobules at the vesical orifice*. We believe that our simple cold cutting punch with coagulation by a single electrode of the individual bleeding points, is still the method of choice, and certainly less dangerous and equally effective.

**Adenomatous Enlargement or Hyperplasia of the Prostate.**—As stated in the preliminary discussion of the anatomy and pathology of the prostate, the lateral and median portions are the regions principally involved in the development of adenomatous spheroids which lead to obstructive conditions. As further stated, it is remarkable that the glands immediately adjacent to the urethra are those in which these adenomata occur, the lateral, posterior and anterior lobes of the prostate rarely taking part in the pathological process known as prostatic hypertrophy.

The symptoms depend upon the location of the lesion, and the mechanical disturbances produced by it. In many cases a prostatic hypertrophy may grow to considerable size without causing much obstruction, difficulty, urinary frequency or troublesome symptoms. In other cases the development of even a small lobe, particularly in the median portion pos-

teriorly beneath the vesical neck, may lead to rapid obstruction with severe concomitant symptoms. We have seen many cases in which a minute lobule caused complete retention, great dilatation of the ureters, kidney pelves, thinning of the renal cortex, and severe local and general symptoms. On the other hand, we have frequently encountered huge lobes weighing 100 Gm. or more in which micturition was disturbed very little, the residual urine slight, the impairment of the upper tract negligible. It is only by the most careful examination, using the palpating rectal finger and urethral instrumentation, cystourethrography, as well as urography, that a discovery of the actual condition present often may be made. The difficulty and frequency of urination, occasional pain and rarely hematuria are the symptoms which usually bring the patient to the doctor. Not infrequently the enlargement has already become great and residual urine and back pressure effects have produced marked changes without the patient realizing that anything serious is present. If patients could be persuaded to undergo systematic examination every year after passing the age of fifty or fifty-five, many cases of prostatic obstruction would be discovered before serious obstructive conditions have arisen. At the same time cases of early carcinoma of the prostate would be discovered. Patients should be warned that with the onset of difficulty and frequency of urination, or even hesitation and smallness of the stream, they should notify their physicians. When loss of appetite or occasional nausea, headaches and dizziness, one or all, come on, an incipient uremia may be present. One should acquaint his clientele with the importance of these symptoms, so that an early diagnosis of prostatic obstruction may be made.

Urine of low specific gravity may indicate renal impairment. The presence of bacteria, which frequently arrive without the passage of instruments, accompanied by pyuria, sometimes by fever, chills, etc., are danger signals which should lead to a careful investigation. In the study of these cases one should at once palpate and percuss the region of the bladder, after the patient has voided, to determine the presence of vesical distention and large residual urine. If such is discovered immediate catheterization is usually contraindicated (more of this further on). On rectal examination the prostate

is carefully examined for changes in size, contour and consistence. In some cases there may be little or no change, abnormality, enlargement recognizable by rectum, whereas great lobes may have forced their way through a dilated sphincter into the bladder where they can be easily recognized by the cystoscope or by urography.

If a markedly indurated area is found in the prostate, even though definite globular elastic hypertrophy is present elsewhere, one must consider the possibility of carcinoma being present, as will be discussed more fully later on. When a palpably distended bladder is made out, one should not pass a catheter unless it is possible to hospitalize the patient and undertake gradual decompression if considerable overdilatation of the bladder is discovered. Complete emptying of a greatly distended bladder through a catheter may lead to hemorrhage, a rapid drop in blood pressure, anuria, uremia and sometimes to a rapidly fatal ending. We have seen over a dozen cases in which the complete emptying of a bladder with marked residual urine was followed by a rapid exitus. (We are sorry to see that the need of this care is poohpoohed by a recent writer.)

It is needless to point out the necessity of great care to avoid infection. Not only should the penis externally be cleansed with care, but the urethra itself should be washed out so that when a sterile catheter is passed no infection will be carried in with it. One should have various types of catheters, not only the rubber or Nélaton catheter, but one with a small coudé or elbowed tip in order to ride up over median enlargements, as coudé or bi-coudé gum catheters of different size may also be required before an instrument is successfully introduced. Metal instruments, even those with an enlarged prostatic curve, may prove dangerous and should be used with care. All practitioners, who are likely to encounter cases of acute retention of urine, should be provided with the proper armamentarium, but also be sufficiently acquainted with the technic and difficulties of catheterization. Great harm can be done by careless methods, and severe complications produced, particularly on the introduction of micro-organisms. The use of the catheter, whether intermittently or inlying, to combat obstruction, residual urine, infec-

tion and other complications associated with prostatic hypertrophy is a chapter in itself, and can only be alluded to here. Suffice it to say that expert methods should be invoked early in all cases of prostatic enlargement with pronounced obstructive conditions. The development of renal function tests, particu-

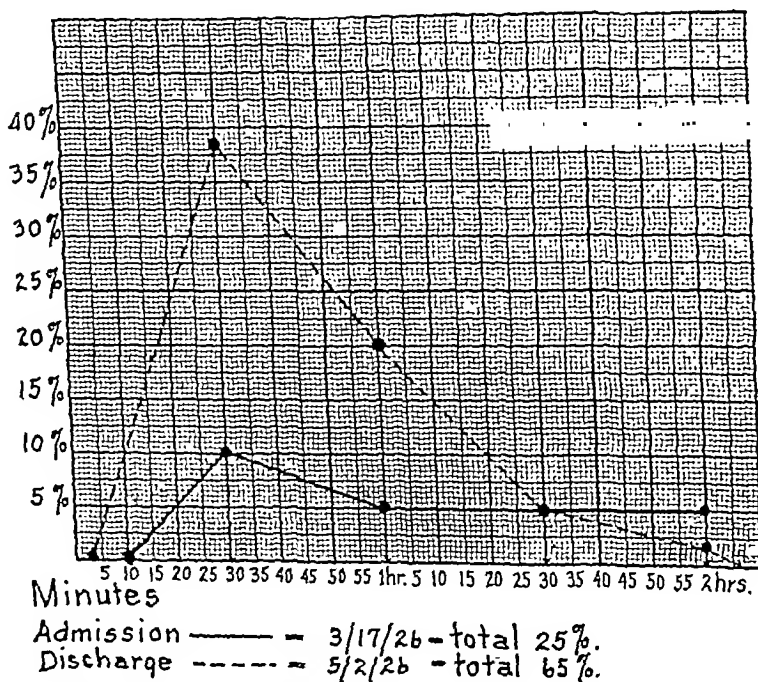


Fig. 105.—Young's phthalein chart for recording appearance time and percentage output of phthalein every half hour. The lower curve in solid black lines shows the phthalein test on admission in a patient with marked obstruction to urination. Appearance time, ten minutes; output first half hour after injection, 10 per cent. Total in two hours, 25 per cent. The broken lines show the phthalein curve after continuous drainage with a catheter for six weeks. Appearance time, three minutes; output first thirty minutes, 37 per cent. Total in two hours, 65 per cent. Prostatectomy successful.

larly the phthalein test taken at half-hour intervals (Fig. 105), always through a catheter if residual urine is present, and the blood chemistry, which parallels inversely the phthalein estimations, are of great value.

*Therapy.*—In a few cases, a considerable enlargement of the prostate may require no surgical treatment. If the patient

voids freely with no increased frequency or pain, and the blood chemistry, phthalein test and cardiovascular system are negative, the patient may often be allowed to go without operation under the surveillance of his physician. Usually, however, the increase in residual urine and the development of obstructive symptoms make some therapeutic measures necessary. In rare instances prostatic massage may for a time be effective, but one must be sure that the function of the kidneys is not becoming impaired and that the cardiovascular system is not endangered by waiting. In most cases of obstruction due to adenomatous enlargement of the prostate when the symptoms are definite and progressive, operative intervention is indicated.

There is no place here to discuss in detail the procedures which may or should be employed. In our humble opinion, only when the prostatic enlargement is largely confined to the median portion posteriorly is transurethral resection preferable to prostatectomy. Transurethral resection is not generally the simple operation that many have considered it, especially in the hands of the beginner.<sup>8</sup> Its widespread usage throughout the profession has led to hundreds of unnecessary deaths. When carefully done by men who have already gained the experience necessary (often by losing a good many patients) transurethral resection may even be repeated in the larger cases several times with fairly good results. As the statistics of Alcock show, the mortality increases with the size of the prostate, and while the second and third operations may not show the mortality of the primary procedures, nevertheless they add to the sum total of fatalities. After careful consideration of the subject, we are convinced that in many cases the prostatic obstruction is of a size too great for the punch operation or methods usually called transurethral resection. In these cases exposure of the prostate through the perineum, and enucleation from within of the adenomatous masses is the safest, surest and most effective method of handling these cases. Statistics and further arguments will be found in various books on Urology.<sup>8</sup> Suffice it to say that in experienced hands the mortality is practically nil; in fact, the last four resident urologists at the Brady Urological Institute had a combined mortality in 160 cases of a little over 1 per cent, and one resident had 58 consecutive cases (which included



his very first case) without a single death. These statistics show the effectiveness of modern methods in the surgical treatment of these benign obstructive conditions.

**Carcinoma of the Prostate.**—Some twenty-five years ago we brought out the announcement which astounded many, viz., that one patient out of five who came with prostatic obstruction was suffering from carcinoma of the prostate, and that in 50 per cent of these cases hypertrophy of the lateral and median lobes was present. Further statistics soon proved our findings were correct, but not until the last two years have we known that carcinoma of the prostate is even more frequent than we had previously supposed. In independent studies of prostate specimens that came routinely to autopsy, two investigators, Rich and Moore, have found that carcinoma of the prostate was present in over 14 per cent of the cases. In 292 consecutive autopsies on males, fifty years or more of age, dying from a wide variety of causes on the medical, surgical and urological services of the Johns Hopkins Hospital during the past three years, Rich says that frank carcinoma of the prostate was found in the routine microscopic section taken at autopsy in 41 cases (14 per cent). Moore found cancer in the prostate at autopsy in 21 per cent of patients over forty-one years of age. His material was obtained from autopsies at two hospitals in Vienna in 1931 and 1932. In both instances consecutive prostate specimens were studied, and in the majority of cases no indication or suspicion of the presence of carcinoma had been present. Both investigators found that the region involved was the posterior lobe in the large percentage of the cases. Moore found that carcinoma of the prostate was three to four times as common as carcinoma in any other deep-seated organ.

Such being the case, it is incumbent upon the medical profession to try by physical examination to recognize these cases early, because we have shown that by means of the radical operation these patients can be cured without much danger or difficulty. Unfortunately, carcinoma of the prostate is symptomless and often extensive before the patient appears for medical advice. In some cases the concurrent presence of hypertrophy may bring the patient for examination fairly early. In a number of cases we have recognized the presence of

carcinoma when we discovered a small, very hard nodule in the posterior, subcapsular portion of the prostate on routine examination with a finger in the rectum (Fig. 106). If patients beyond fifty years of age could be subjected to early examination of the prostate many early cases of carcinoma would be detected. Induration of third degree, *i. e.*, very great hardness, usually accompanies carcinoma. As the lesion is generally situated beneath the posterior capsule of the prostate, it can be readily felt. An *x*-ray will exclude stone. Cystoscopy may reveal the presence of enlarged median or lateral lobes, but one should not be deceived by this evidence of benign adenomata, because as stated above, the two are frequently concomitant.

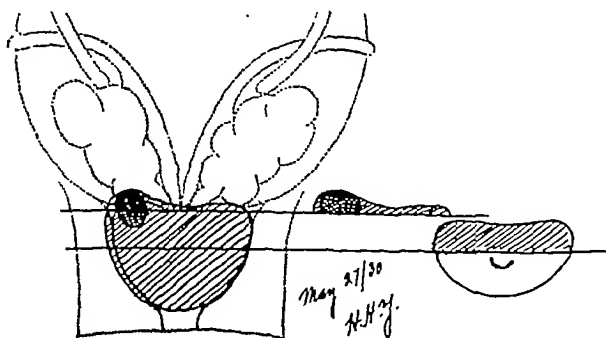


Fig. 106.—Small carcinomatous lobule in left lobe. This nodule was moderately elevated, of third degree induration. There was very little obstruction to urination. A hemiprostato-vesiculectomy was performed. The patient is well now over five years. (BUI 19552.)

When one discovers a hard nodule, which does not show a shadow with the *x*-ray, one should usually make certain that this is not carcinoma by an expert study of the case. By exposing the prostate through the perineum an excellent view is obtained, at which it is possible to palpate the suspicious region, incise it if necessary and excise a portion for biopsy. In most cases the presence of an extremely indurated area may be recognized as carcinoma, and the radical operation, which we have now carried out in over 60 cases, may be easily performed with little risk. Our statistics show that more than 50 per cent of the cases, which have been followed five years or more since leaving the hospital, have been radically cured.

Statistics from other clinics have confirmed our view that carcinoma of the prostate, if discovered sufficiently early, is an easily curable disease. The fact that the organ is surrounded by three encapsulating fasciae prevents the spread to adjacent structures for a considerable time, and therefore adds materially to the possibility of obtaining radical cures by extensive operative excision. If the medical profession could be made to realize the importance and truth of Osler's trite saying that "the difference between a good doctor and a poor one was that the good doctor knew how to make a rectal examination," and make rectal examinations a routine procedure in elderly men, many cases of carcinoma of the prostate would be detected sufficiently early for radical cure. Success in the treatment of carcinoma of the prostate depends upon the diligence and acumen of the general practitioner and the decision of operators not to relegate these patients to palliative procedures when a chance of radical cure is at hand.

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## CLINIC OF DR. FRANCIS F. SCHWENTKER

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### THE USE OF SULFANILAMIDE IN THE TREATMENT OF INFECTIONS

**Preface.**—The past two years have seen the introduction of a startling, new chemotherapeutic agent, sulfanilamide. Its great promise has initiated an extensive investigation of its properties but there is still a great deal to be learned. The time has come, however, when a brief summary of the existing practical knowledge of this drug should be presented to the medical profession. It should be clearly understood that what has been written in this article reflects only the relatively meager present knowledge of sulfanilamide and that further investigation may alter the opinions and conclusions presented.

**Synonyms.**—Sulfanilamide is the name given by the Council on Pharmacy and Chemistry of the American Medical Association to the compound, para-amino-benzene-sulfonamide. The drug is marketed by a number of firms under the proprietary names of prontosil, stramid, streptocide, colsulanyde, sulfamidyl and sulfonamid P.

**Historical.**—In 1935 Domagk published in Germany a report of the effect on experimental streptococcal infections in mice of an azo dye called "prontosil." The bactericidal properties of this dye for the  $\beta$  hemolytic streptococcus were so definite that its use in human infections rapidly followed. In a short time the compound was being extensively studied throughout Germany, France and later in England and the United States. It soon became apparent that the chemotherapeutic action was not a property of the whole molecule but was inherent in the para-amino-benzene-sulfonamide radical, the azo dye being without effect. It was demonstrated that

when prontosil is administered to patients or animals, the molecule is broken down by the body so that the active portion, para-amino-benzene-sulfonamide, is released from the inactive dye fraction. Since the dye itself tints the patient a vivid orange hue and is irritating to the gastro-intestinal tract, its use is rapidly being discontinued and prontosil is being replaced by sulfanilamide.

It is of interest that after the chemotherapeutic effect of para-amino-benzene-sulfonamide had been demonstrated it was recalled that the compound had been known since the latter part of the nineteenth century and as long as twenty years ago was studied for possible bactericidal effect against the pneumococcus. Apparently no one tested its activity against streptococci until it was indirectly rediscovered as described.

#### RESULTS IN VARIOUS INFECTIONS

**Beta Hemolytic Streptococcus.**—Up to the present time the greatest field for usefulness of sulfanilamide has been in infections due to the  $\beta$  hemolytic streptococcus. This includes a large number of illnesses and it may be of interest to mention a number of them specifically.

The results with *erysipelas* have been particularly satisfactory. Following instigation of treatment the patient's temperature falls rapidly to normal and the pain in the affected area is markedly reduced. The persistent spread of the lesion, so characteristic of *erysipelas*, is checked with dramatic suddenness but the eruption already present clears with only the usual speed. The results with infants, particularly newborns, in whom the mortality has always been high, are especially gratifying since the majority of these patients now recover.

*Streptococcic septicemia* carries a high mortality rate and even in those cases where recovery follows, the tendency to abscess formation usually prolongs the illness markedly. It has therefore been gratifying to find that in most cases the blood stream becomes sterile in twenty-four to forty-eight hours after the instigation of sulfanilamide therapy. The tendency to form metastatic foci is also reduced. The same good results have been seen in *streptococcic meningitis* and the rapid sterilization of the spinal fluid in a disease which has heretofore

resisted all attempts at therapy is particularly striking. In Baltimore alone there are records of 19 recoveries in 23 cases and from other cities come similar reports.

The results in *streptococcic tonsillitis* have been good but not striking, probably because the disease is usually mild and of short duration. When the infection is marked and progressive, however, sulfanilamide therapy causes a rapid decline in the severity of the disease. If treatment is begun with *peritonsillar abscess* before the lesion has broken down to fluctuancy, the condition usually retrogresses without the necessity for surgical evacuation.

The average case of *scarlet fever* is so mild that sulfanilamide causes no appreciable acceleration in the improvement rate. It must be remembered that the drug has no antitoxic property and therefore cannot be expected to replace streptococcus antitoxin in neutralizing the toxic effects of a severe infection. When, however, the focus in the throat is severe and more especially if it is progressive, sulfanilamide is indicated as an adjunct to streptococcus antitoxin; the latter to neutralize existing toxin and the former to check the infection.

Although sulfanilamide is apparently of little therapeutic value in the average acute case of scarlet fever, it has proved of definite aid in the treatment of those complications of scarlet fever which are bacterial in origin, especially *otitis media*, *mastoiditis* and *adenitis*. In fact, these conditions respond well to sulfanilamide therapy whenever they are caused by the  $\beta$  hemolytic streptococcus whether associated with scarlet fever or not.

In acute or chronic *osteomyelitis* of streptococcal origin sulfanilamide is indicated. It should be emphasized, however, that when the focus of infection is in bone, whether mastoid cells or other osseous tissue, the therapy should be continued for two weeks after a clinical cure has been accomplished. Otherwise relapses are common.

When *puerperal fever* is due to the  $\beta$  hemolytic streptococcus good results may be expected following sulfanilamide therapy.

Although the majority of infections due to the hemolytic streptococcus show rapid improvement, for some reason yet

unknown, in an occasional case sulfanilamide is without any apparent therapeutic effect.

**Streptococcus Viridans.**—Unfortunately, the results of sulfanilamide therapy with other types of streptococci have not paralleled those with the  $\beta$  hemolytic type. When used in viridans infections the drug apparently inhibits the growth of the organisms and fewer colonies are found in blood cultures but even under intensive therapy no cures have been effected.

**Pneumococcus.**—The status of sulfanilamide as a chemotherapeutic agent in pneumococcal infections is still uncertain. Experimental work has shown that the drug is at least bacteriostatic, if not bactericidal, and that its effect varies with different types of pneumococci. Best results have been obtained with type III infections. Clinically the drug has been used intensively only in pneumococcic meningitis. In these cases there is a definite prolongation of survival time with occasional recovery but the results have been nowhere nearly so good as with streptococcic meningitis. However, in a disease with such an overwhelming mortality sulfanilamide seems indicated, at least until some better form of therapy is discovered.

**Meningococcus.**—Preliminary experimental work with mice has shown that sulfanilamide affords these animals even greater protection against meningococci than against streptococci. We have treated to date 52 consecutive, unselected cases of meningococcic meningitis with sulfanilamide alone, without antiserum. The mortality in this group was 15 per cent, a figure which compares well with the 30 per cent mortality among serum-treated cases seen during the same epidemic in the same hospital. Certainly, no wide conclusions can be drawn from 52 cases but there seems little doubt that the drug is at least as effective in meningococcic meningitis as is antiserum and has none of the disadvantages due to foreign protein.

These conclusions are confirmed by experimental work which has further shown that when sulfanilamide therapy is combined with antiserum injections a synergistic effect apparently takes place. The protection of mice against meningococci by the combined treatment is far greater than one would expect from the protection afforded by each method



alone. Only further clinical trial will establish the best method of treatment.

**Gonococcus.**—The similarity of the gonococcus to the meningococcus has precipitated a trial of sulfanilamide in gonococcal infections. Because the organism is of low virulence for laboratory animals no experimental evidence exists but reported clinical trials indicate a definite value for the drug in cases of acute urethritis in the male. The results in gonorrheal ophthalmia have, in our experience, been indifferent and no data have yet been published concerning the effect in gonorrheal vaginitis.

**Bacillus Coli.**—Helmholz has recently reported excellent results in the treatment with sulfanilamide of *pyelitis* due to the colon bacillus or the staphylococcus. No therapeutic effect could be demonstrated, however, when the pyelitis was caused by *Streptococcus faecalis*. He considers the drug superior to any other urinary antiseptic.

**Bacillus Welchii.**—Recent experimental and clinical trials have produced some evidence that sulfanilamide is also helpful in the treatment of gas gangrene.

**Other Infections.**—It is manifestly impossible in the short time since the introduction of sulfanilamide to test its chemotherapeutic effect in all types of infections. At the present time one can say only that value has been proved for the drug in infections due to the  $\beta$  hemolytic streptococcus, and that favorable evidence exists with the meningococcus, the gonococcus, the gas bacillus, and the colon bacillus (at least in urinary tract infections). Results with the influenza bacillus have been disappointing. There is some experimental evidence that the drug is helpful in typhoid infections. No reports have been published on its use in infections due to protozoa, spirochetes and the filtrable viruses.

#### METHOD OF TREATMENT

Sulfanilamide is supplied in two forms, tablets (5 and 7½ grains) for oral administration and powder for parenteral injection. The powder is administered as a 1 per cent solution in physiologically normal saline and is prepared by dissolving 1 Gm. of sulfanilamide and 0.85 Gm. of sodium chloride in each 100 cc. of distilled water and warming slightly to effect

complete solution. The mixture is sterilized by autoclaving. At least one commercial company is also supplying sulfanilamide sterilized in ampules in dry form much like arsphenamine. The content of an ampule is added to the required volume of sterile normal saline and the mixture heated slightly to promote solution. No matter what method is used, the sulfanilamide tends to settle out of solution after twelve to eighteen hours. This difficulty is overcome simply by warming the mixture so that the drug is redissolved. Repeated injections of such solutions can be given subcutaneously or intraspinally without any local or systemic reaction.

The method of treatment is, with certain limits, the same for all diseases. The objective is to produce and maintain in the tissue fluids, particularly those at the site of infection, a therapeutically effective concentration of sulfanilamide. To accomplish this result two conditions must be fulfilled; first, adequate amounts of the drug must be given, and secondly, the administration must be repeated frequently enough to replace the sulfanilamide excreted by the body.

The dosage of the drug is also the same, no matter what disease is being treated, but varies according to the weight of the patient and the severity of illness. In the tabulation is given the daily dosage for patients of different age groups.

TABULATION  
SUGGESTED DOSAGE OF SULFANILAMIDE

Infection.	Total daily dosage.			
	Grams.		Number 5-grain tablets.	
	Mild.	Severe.	Mild.	Severe.
Infants —up to 40 pounds	0.9-1.5	1.8-3.0	3- 5	6-10
Children —40 to 80 pounds	2.1-2.7	4.2-5.4	7- 9	14-18
Older children—80 to 120 pounds	3.0-3.6	6.0-7.2	10-12	20-24
Adults —over 120 pounds	3 6-4.8	7.2-9.6	12-16	24-32

Daily doses are divided for intervals of four to six hours.

For ordinary mild infections such as streptococcic tonsillitis, erysipelas, pyelitis and so forth, the amount administered will vary from 0.9 Gm. per day in the infant to 4.8 Gm. in an adult. When the infection is severe enough to threaten life, such as in streptococcic septicemia or the meningitides, the daily dosage is doubled.

A general plan of treatment is to initiate the therapy by giving a full twenty-four-hour dose at once and then continue administration in fractional doses every four or six hours. For example, an older child with mild erysipelas might receive 12 5-grain tablets (3.6 Gm.) by mouth and thereafter 2 tablets every four hours. By this method a therapeutically effective concentration of sulfanilamide is produced in the blood within four hours and will be maintained at a fairly constant level as long as the treatment is continued.

The same general plan is maintained when sulfanilamide solution is injected subcutaneously except that, since it is impractical to give subcutaneous injections at four- or even eight-hour intervals, the drug is given every twelve hours. For example, an unconscious adult seriously ill with streptococcic meningitis would receive a subcutaneous injection of 960 cc. of the 1 per cent solution (9.6 Gm.) at the time of admission and 480 cc. (4.8 Gm.) every twelve hours thereafter until improvement was evident.

Intraspinal injection of the drug may be given when the infection involves the meninges. The method of administration is the same as that usually employed for injections of serum. In cases of meningitis the patient is usually treated intraspinally every twelve hours until definite improvement is seen. Thereafter, the drug is administered only by mouth or, if necessary, by subcutaneous injection. Since volumes no greater than 10 cc. to 30 cc. can safely be injected intrathecally, the spinal route must be considered only as an adjunct to oral or subcutaneous injection. In fact, since sulfanilamide is rapidly excreted into the spinal fluid, and in concentration closely approaching that in the blood, there is some question whether the intraspinal route is necessary.

The problem frequently arises as to the best route for administration. Analyses have shown that the concentration of sulfanilamide in the blood reaches as high a peak and as

quickly when the drug is given by mouth as when it is injected subcutaneously. For this reason sulfanilamide is always administered orally whenever the patient can take the pills. Only in unconscious persons, or those otherwise unable to swallow tablets, is subcutaneous injection necessary. The oral route also has the advantage that the intervals between doses are smaller and the concentration in the tissue fluids is therefore kept at a more constantly effective level. In certain cases it may be advantageous to combine oral therapy with subcutaneous injections. When this is done the same daily dosages previously recommended are followed, the amounts of sulfanilamide given by each route being added together to compute the total dose. It should be emphasized, however, that no matter by what route or routes the drug is given, the times of administration should be spaced as nearly in intervals of four or six hours as possible.

Although sulfanilamide may be given in empirical doses according to the method outlined, we have found it advantageous, at least in seriously ill patients, to control the treatment by analysis of blood and other body fluids for sulfanilamide. Marshall and his co-workers have recently described<sup>1</sup> a simple method for analysis which can be performed in any clinical laboratory. Since sulfanilamide is rapidly absorbed after administration and also rapidly excreted, it is necessary to collect specimens of blood for analysis at some fixed time after administration of the drug. A peak in the concentration of sulfanilamide in the blood usually occurs about four hours after administration. For this reason we routinely obtain a sample for analysis four hours after the first administration of sulfanilamide and again the following day four hours after any dose. From the values obtained on analysis it is possible to be assured that the sulfanilamide is being absorbed properly and furthermore to regulate the dosage in order to maintain a therapeutically effective concentration in the body fluids. For mild infections we consider a concentration of 6 mg. per 100 cc. adequate but in severe infections a level of 10 to 15 mg. per 100 cc. should be maintained.

<sup>1</sup> Jour. Amer. Med. Assoc., 108: 953, 1937.

## DISCONTINUANCE OF TREATMENT

Every case presents a new problem in determining when to discontinue treatment with sulfanilamide. As a general rule administration of the drug can be stopped when the patient has been free of symptoms and fever for two or three days. In this connection, however, one must remember that sulfanilamide itself sometimes gives rise to a febrile reaction. In cases like meningitis and septicemia where one can culture a focus of infection, treatment should be continued until the cultures on two or three consecutive days are sterile. Where bone has been involved therapy should be continued for two weeks after a clinical cure has been accomplished in order to prevent relapses. In any case it is helpful to taper off the dosage of drug over a two- or three-day period.

## MODE OF ACTION

Very little data have accumulated to explain the exact means by which sulfanilamide effects its chemotherapeutic properties. When used *in vitro* the drug inhibits the growth of susceptible organisms but it apparently has no bactericidal power on organisms already present. There is no evidence that phagocytosis is stimulated in any way. At the present time it seems probable that sulfanilamide merely inhibits multiplication of the bacteria so that the protective mechanisms of the body, such as phagocytosis, are able to deal with something less than an overwhelming number of organisms.

## TOXIC EFFECTS

The total experience thus far gained in the use of sulfanilamide is not yet sufficient to establish the exact status of its toxic effects. In the light of our present knowledge, however, it may be considered a relatively harmless drug. The average patient will show no disturbing symptoms, but in a few persons there will develop certain toxic manifestations with which the physician should be familiar. Happily none of these has as yet been serious; some can be disregarded entirely and the remainder are amenable to treatment.

**Usual Symptoms.**—Most patients who receive sulfanilamide complain of a feeling of light-headedness usually de-

scribed as "whoozy" or "drunk." Associated with this may be ringing in the ears, headache, a slight temporary loss of mental acuity and at times tingling or other paresthesias. None of these symptoms is serious and they can and must be disregarded if treatment with sulfanilamide is to be carried out. On the other hand, the frequent occurrence of these symptoms, coupled with the fact that they are considerably ameliorated when the patient is kept in bed, has given us the opinion that sulfanilamide therapy should not usually be carried out on ambulatory patients.

**Cyanosis.**—By far the commonest of the toxic manifestations is cyanosis. It develops in over half of the patients who receive the drug and varies from an almost imperceptible blueness of the mucous membranes to a deep cyanosis. From the viewpoint of the patient and his relatives it is certainly the most alarming symptom because popular knowledge connects cyanosis only with approaching death. Actually the condition appears to be quite harmless and can be ignored entirely. The mechanism of the cyanosis is not yet clear. In some cases it appears to be due to sulfhemoglobinemia but in others it may be due to the formation in the blood of some compound which imparts a blue color to the mucous membranes. There is apparently considerable variation between different patients in their reactions in this direction. Some persons develop cyanosis on very small doses of sulfanilamide and others remain free even when receiving the drug in large amounts.

**Rash.**—About 6 per cent of patients who receive sulfanilamide develop a rash, usually between the tenth and fourteenth days of therapy. The eruption is almost a replica of the measles rash and is usually accompanied by fever and malaise. It fades rapidly when the drug is discontinued and will reappear in modified form if therapy is resumed. Whenever rash develops in a person receiving sulfanilamide, treatment with the drug should be stopped. Fortunately, in most cases the eruption does not appear until late in the course of therapy, at a time when convalescence has usually begun and the treatment can safely be discontinued. In those few cases where life was threatened we have disregarded the rash and continued treatment, apparently without untoward results.

**Fever.**—Occasionally fever develops during sulfanilamide

therapy. When possible the drug should be discontinued but if necessary the fever may be ignored.

**Acidosis.**—Acidosis, in some degree, develops not infrequently in patients under sulfanilamide therapy. In most cases it is so mild as to cause no symptoms but in a few the signs of acidosis are classical. The diagnosis may be verified by demonstration of a lowered  $\text{CO}_2$  combining power for the blood. Rarely this falls to 20 volumes per cent, usually it is between 35 and 40. The acidosis is apparently due to a loss of base in the form of sodium and potassium in the urine. When the condition occurs it may be easily combated by the administration of sodium bicarbonate by mouth or sodium lactate solution parenterally. As a preventive measure sodium bicarbonate may be administered with the sulfanilamide. An adequate routine is to give 5 grains of sodium bicarbonate by mouth for every 5 grains of sulfanilamide administered up to a maximum of 10 grains at each dose.

**Acute Hemolytic Anemia.**—A rare complication we have seen is acute hemolytic anemia. For some reason not yet clear an occasional patient will show a drop in red blood cell count and hemoglobin value. This may be very rapid. In one of our patients the hemoglobin fell from 85 to 30 per cent in three days. Some patients show hemoglobin in the urine at the same time. The rapidity with which hemolytic anemia can come on makes it imperative to watch closely the erythrocyte count or hemoglobin content of the blood of all patients receiving sulfanilamide. Should the condition develop it can be checked immediately by discontinuing the drug. In severe cases or where it is necessary to continue treatment with sulfanilamide, transfusions may be used to control the hemoglobin level. No case has yet come to attention where the blood destruction was not immediately checked when the sulfanilamide administration was stopped.

**Other Toxic Effects.**—Several cases of *granulocytopenia* have occurred among patients receiving sulfanilamide. This complication is extremely rare and apparently occurs only in persons who have received the drug for several weeks. A few deaths have occurred but in the 2 cases of which we have direct knowledge improvement followed as soon as the drug was discontinued. The possibility and the seriousness of this

complication make it imperative to follow the blood leukocyte count at least every two days.

*Jaundice* has been known to occur during the course of treatment with sulfanilamide but too little is known about the exact nature to justify further discussion.

The earlier reports on prontosil therapy mentioned that albumin, a few red blood cells and casts were commonly found in specimens of urine from patients receiving the dye. We have never found this condition in cases where sulfanilamide was used. The kidneys of patients who died of their disease while receiving sulfanilamide have never shown any gross or microscopic changes which could be attributed to the drug. In fact this is true of all other organs as well. In general, however, when a definite nephritis exists it would seem better not to treat the patient with sulfanilamide especially if there is nitrogen retention. When the infection is of such serious nature that life is threatened the drug may be used even in the face of nephritis if the blood is frequently analyzed for sulfanilamide and the dosage regulated to maintain the usual effective concentration. The damaged kidney excretes sulfanilamide less rapidly than a normal organ. For this reason smaller doses of the drug will usually be necessary.

A recital of the toxic effects which may occur during treatment with sulfanilamide should be convincing evidence that the drug is not a completely harmless medication. It should not, therefore, be used indiscriminately. When the  $\beta$  hemolytic streptococcus is known to be the cause of an infection of more than mild degree, sulfanilamide is indicated. In certain cases of gonococcus, meningococcus and gas bacillus infection and in pyelitis due to *Bacillus coli* or staphylococcus the drug may be of definite value. But at the present time the evidence for its use in other infections is insufficient to justify its general clinical use, at least until further investigations have clarified the problem. Nothing will bring this promising drug into disrepute more rapidly than widespread indiscriminate use.



## CLINIC OF DR. JOHN TILDEN HOWARD

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#### MEDICAL AFFECTIONS OF THE COLON

##### SIMPLE CONSTIPATION

SIMPLE constipation is a problem in the sanitary engineering of the body which I wish to discuss first. One thinks of simple constipation as either too infrequent evacuations of the bowel or as subjectively incomplete evacuations when there is no organic obstruction, no anal fissure, and no intra-abdominal inflammation to cause reflexly the constipation. All of us know persons in very good general health who have a stool only once in three or four days and, unless they complain of the condition, we leave well enough alone and say that we are not all cut according to the same pattern, though we are from the same cloth. However, under the conditions of modern life and with lay opinion as it is, the frequency of bowel evacuation should probably be at least once each day. The amount of fecal matter passed is unquestionably determined by the kind and amount of food eaten and it is my impression that, in the absence of organic obstruction or of impaction, the sensation of an insufficient stool is produced by sigmoidal or rectal spasm rather than by actual fecal retention. Simple constipation, as I see it, is not a penalty which we have to pay for the erect posture of the body; it is not related to ptosis or to redundancy of the colon; it is a penalty which we pay for our civilized social and economic system. Besides eating our excessively refined foods, we work so hard and worry so much! We work and worry not only for and about ourselves, but also for and about our children and our grandchildren.

We all know that those little barbarians, our own offspring, for the first few years of their lives have practically no constipation if they are decently fed. Mothers and nursemaids in

a mysteriously simple way train the little "animals" to open their bowels with remarkable regularity, as they train them to retain their urine until they have toilet facilities at hand. At the age of four or five these little Bushmen attend school and there they begin to appreciate the strains and repressions of our society and they may become constipated. Perhaps that unhappy day is deferred to adolescence or to the time of marriage or to a time of economic depression and worry or to the period of pain and strain of a surgical operation. Sooner or later a fair percentage of our patients (more females than males) becomes more or less constipated and asks our advice. My own experience confirms the popular medical conception that 95 per cent or more of constipation is of the spastic type; it is an expression of excessive bowel tone at some point or points and this hypertonicity is produced through the nervous system. Fatigue, irregular habits, economic worry, repressed emotions, and insufficient intake of food, all are important in upsetting the automatic function of the colon, balanced as it is between two opposing systems of control: one stimulating, the other inhibiting. The stimulator is, broadly speaking, the parasympathetic system with the vagus and sacral nerves. The sympathetic system with its splanchnic nerves is the inhibitor. It is only fair to admit that the delicate balance between sympathetic and parasympathetic systems may be upset reflexly by inflammatory processes within the abdomen and in that manner constipation may become a symptom of some other disease process. In these conditions the subordinate rôle of the constipation is usually recognized by the physician and it is treated with the remedy for the primary condition. Lane's kink, Jackson's membrane, and other conditions which produce actual organic stenosis of the bowel seem to be properly included under the heading of organic intestinal obstruction and, therefore, they are in the realm of the surgeon. Careful physical examination and a complete history usually make the separation of organic obstructions from the functional cases relatively simple. However, observation while the patient is on treatment is necessary at times and it may be very helpful in diagnosis.

**Treatment.**—The treatment of simple constipation should begin with the assumption that it is spastic and, as I have said,

the chances are 95 in 100 that the hypothesis is correct. The patient may be told (with considerable satisfaction to him) that he has an obstructive type of constipation but that the obstruction is caused by a spastic area or areas in the colon and that these spastic areas result from an imbalance in the sympathetic nervous system, that these areas are usually in the sigmoid or descending portions of the bowel and that they may have caused dilatation and atony of the right half of the colon by producing relative obstruction on the left side. When the spasm is relaxed, then tone will return to the cecum and ascending colon for the resistance in the terminal portions of the bowel will be reduced. This is a working explanation of the mechanism of the constipation and the intelligent patient will usually welcome it. When the patient understands what we are trying to do, he will be more co-operative in the elimination of irritant laxatives and enemata. Occasionally I say, "Your gastro-intestinal tube is phylogenetically one of the most primitive and elemental structures of your body. For thousands of years the ancestors of the intrinsic nerves and muscles of your intestinal tube propelled its content caudalward and, though you have been constipated for twenty, thirty, or forty years, your bad habits of spasm over two, three, or four decades haven't displaced the hereditary habits that have been established through the ages in the intrinsic nerves of the intestine itself. Could you survive decerebration, my dear patient, your intestine would function as well as that of the earthworm." This last remark is made, of course, only to selected patients. To stupid persons such explanations as I have mentioned are useless and one must dispense orders like a drill sergeant. To the intelligent, one should try to be reassuring and to get a concept of the cause of the constipation into the patient's mind. Then the battle is half won; the patient is no longer afraid of acute obstruction and serious results from his constipation.

Rest and freedom from strain are very important therapeutic measures. Frequently a camping trip or a few days at the seashore is all that is needed to give normal colonic function. Then, believing that mechanical and chemical irritation of the colon with bran, nuts, and other coarse forms of cellulose and with irritant laxatives aggravates the spasm, we put

the patient on a diet in which the cellulose content is high but in which it has been softened by cooking (the well-known smooth diet), and we stop the use of irritant cathartics and irritant enemata. We may give prunes, flake agar, or one of the newer proprietary forms of threshed psyllium seed to add soft bulk to the stools. Mineral oil by mouth and retention enemata of warm cotton seed oil are given if they seem necessary. Warm oil by rectum seems to be an excellent antispasmodic for the colon. Exercise short of fatigue is usually recommended but, except in the patient with unusually poor abdominal muscles, special calisthenics are not prescribed. Regular habits of going to stool are encouraged and sometimes a very small enema of normal salt solution or a glycerin suppository is allowed to encourage the action of the bowel at the desired time. I need only mention the glass or two of hot water before breakfast that is deservedly so popular. The after-breakfast cigar or cigaret activates some colons in a manner that I've never understood. Does tobacco really give us relaxation in our keyed-up lives at a time when our colons are ready to perform? Nicotine in small doses is said to exaggerate peristaltic contraction by stimulating the autonomic ganglia. While I don't disparage this treatment, I think that it is too unreliable to advise routinely . . . even though I do own one or two shares of American Tobacco. I have wondered why the advertising firm that promulgated "theol" of tea as an aphrodisiac has neglected its opportunities to promote the sale of tobacco by publishing its allegedly stimulating effect on the bowel.

The completely atonic colon with constipation as the result of atony does occur. In such relatively rare cases one may advise stimulation with branny foods and cascara. We are, however, very wary about the diagnosis of atonic constipation because so many colons that seem to be atonic have spasm in their sigmoidal portions with dilatation behind the spasm.

There are a certain few elderly patients who are recalcitrant to our nonirritant anticonstipation therapy. These patients have used salines for years and they expect several copious watery stools a day in spite of a rather limited low-residue dietary. They insist on large daily enemata or on

salines. One must use judgment in the management of these patients. It would be easy to reeducate their colons but most difficult to reeducate their cerebra in their ideas of bowel function. Therefore, we tolerate Epsom salt, Glauber's salt, sprudel, pluto, Hunyadi, and sal hepatica in their treatment when there is little or no subjective abdominal distress from this treatment of simple constipation. In the management of cholecystitis and a few other abdominal syndromes, the salines do have a place.

### MUCOUS COLITIS

It is only a step from constipation of the spastic type to mucous colitis or spastic colitis or irritable colon or unstable colon; they are all synonyms. From my point of view this condition is either a myxoneurosis or it, less frequently, results from irritation of the bowel with laxative drugs. Rarely it may be called "catarrhal colitis" and represents the residual of a healed ulcerative process. If mucous colitis is cured by the omission of laxatives, it may be said to have resulted from chemical irritation. If the condition follows amebic or bacillary dysentery, it may be said to be a residual from that disease. However, the majority of patients who have this affection have had no organic disease of the bowel and in them the establishment of bowel management without irritant drugs does not produce a real cure. These are congenitally frail persons in whom there has been more or less nervous strain and fear. This latter unhappy state often results from the passage of mucous casts of the bowel and the patient who sees them is certain that a portion of the lining of his gut has sloughed away. There is a diarrheal tendency in these cases and looseness often alternates with constipation as the tone of the colon varies. Gas and more or less abdominal pain (usually on the left side) accompanies the ailment. When a nervous woman complains of "gallbladder pain on the left side," one should always inquire about the occurrence of mucus in the stools and lean toward the diagnosis of irritable colon or renal disease unless evidence for gallbladder trouble, gastric ulcer, or organic disease of the colon is very strong. Because almost any abdominal condition can be simulated by an irritable colon, medical students are taught to rule out all or-

ganic conditions before making that diagnosis or the diagnosis of mucous colitis. That is a good teaching for undergraduates, lest they see an irritable colon alone in patients with acute appendicitis or with carcinoma of the colon. We, however, are probably old enough to diagnose a functional condition of the colon without having too many x-ray examinations. In fact, we must diagnose it without all laboratory tests because few of our patients can afford expensive examinations. I do want to say a word for the simple tests for occult blood on the stools of patients in whom functional colonic disorders are suspected. I am always fearful lest I miss a carcinoma in its early manifestations and a stool that is negative for occult blood to benzidine is a comforting finding in a patient who has been labeled a case of mucous colitis.

To allergy have been laid of late many of man's ailments and mucous colitis has been said to be a manifestation of sensitiveness to food or to bacteria. Some foods do seem to produce edema of the bowel and colonic spasm through an immunity mechanism but these cases are rather rare and, unless the offending food is wheat, milk, or egg, the patient who has real intestinal allergy has usually discovered his idiosyncrasy by the time that he consults his doctor. It is wise to lend a receptive ear to a patient who says that one or two foods consistently disagree with him. As everyone recognizes, the patient who claims that all foods disagree probably isn't allergic to any. We always test obscure intestinal cases for sensitiveness to wheat, milk, and egg and very occasionally valuable leads are given us. Rowe's elimination diets may be valuable in the hands of some; I have had little experience with them. Sensitiveness to colonic bacteria is a most difficult thing to prove. It has been claimed that skin-test sensitivity to a strain of bacteria isolated from the colon indicates an etiologic relationship between that organism and mucous colitis (if the patient has that condition).<sup>1</sup> Short, Dienes, and Bauer<sup>2</sup> made skin tests with strains of *Bacillus coli* and streptococci isolated from the stools of patients with chronic arthritis. They found no real contrast between the arthritic and nonarthritic patients by skin testing. Some of the intestinal strains gave uniformly stronger reactions in all persons tested than did other strains. "Variations in skin-tests may be explained,"

they said, "by differing irritability of patients' skins, natural toxicity of bacterial species, or by sensitization to certain bacterial groups." Though these workers tested arthritics and controls for skin sensitiveness to colonic bacteria, their conclusions concerning the fallacy of skin testing with colonic organisms in patients with chronic rheumatoid arthritis seems to me to apply in cases of mucous colitis. A skin reaction to a bacterial protein is not very conclusive proof of etiologic relationship unless the skin tests are adequately controlled.

**Treatment.**—The treatment of mucous colitis in our hands is moderately satisfactory. Since most of the patients who are subjects of this affection are psychoneurotics, they are improved, but rarely cured, by treatment (unless the spastic colitis has been produced by irritant cathartics). A majority of the patients who we see have previously consulted several physicians and they come to us (and, perhaps, go from us to others) with the hope that they will find someone who will confer on them a condition of perfect health. That beatific state is beyond most of the neurotics in Baltimore and I venture to say that it is so elsewhere. They have inherited and acquired nervous and psychic habits too unstable to react moderately to all stimuli and improvement is all that they can expect from medical treatment. And they can sometimes be remarkably improved! From most intelligent patients can be obtained the major cause of their functional troubles. Financial worry, strain of business, fatigue, domestic discord, disappointments, family illnesses, and thwarted ambition are but a few of the aggravating factors. Their correction or, more often, an understanding of the problem and the necessary adjustment to the unhappy situation give the most relief. Valuable adjuvants are rest, a smooth diet, retention enemata of cotton seed oil, daily doses of barium sulfate, kaolin or bismuth, belladonna and sedatives. Colonic irrigations give temporary relief but in the long run they seem to aggravate spasm. I consider acidophilus milk by mouth as a harmless method of suggestive therapy. With colonic implantations of acidophilic bacteria and with vaccines, I have little patience. Formerly it was usual to label these patients as neurotics and to dismiss them with no attempt to assist them in their distress. With rational treatment we are keeping them away from the

cults and we are doing them good. They may be neurotics, but they are usually intellectuals of a sort and to them is assigned much of the creative and cultural work of the world. There would probably be fewer irritable colons if we were all savages and lived the simple life. Still, most of us would exchange a spastic colon which could be kept quiet by treatment for the privilege of contributing a cultural bit to the world. Like our decaying teeth, the spastic colon is a penalty exacted by civilization from the more temperamental of us.

And here at the borderline of functional and organic colonic affections I must say a word about "auto-intoxication." The presence of intestinal toxemia or the probability of its presence in adult patients with organic lesions of the colonic wall is readily admitted. Whether there is such a clinical entity as "large intestinal auto-intoxication" without ulceration of the bowel is a subject that has long been debated by scientists. Certainly the idea that such a condition commonly exists has been popularized by food faddists, by salesmen of yeast, of beneficent (?) micro-organisms, of intestinal disinfectants (?), and of patent foods. To prove their point the advocates of the attractive theory of intestinal toxemia must show that toxic substances are developed in the colon, that they are developed in sufficient quantities to cause poisoning, that they are not broken down into harmless substances before they go through the intestinal wall, that they do pass through the wall, that they escape destruction in the liver, and that they will produce the symptoms of auto-intoxication when they are given subcutaneously or intravenously. As yet no such substance has met all of these requirements. My own feeling in the matter is that auto-intoxication is theoretically possible, especially when the colonic content is liquid. I believe that it is an excessively rare condition when formed or hard stools are passed; from them much absorption is unlikely. Most of the symptoms of so-called "colonic toxemia" can be relieved with surprising rapidity by mechanically evacuating the bowel (and so changing the stimulus to the sympathetic system). Dr. Alvarez<sup>3</sup> has felt that a true intoxication would not clear so quickly. As he says, "One does not immediately sober a drunken man by taking away his bottle of whiskey." We have all seen indicanuria disappear mysteriously by relief of emo-



tional tension or change of scene; there the principal rôle must have been played by the nervous system. The body's protective mechanism is a very efficient one and when we realize that we can ingest myriads of bacteria (even pure pus) and tetanus toxin and many chemicals without doing much harm, we wonder at the barriers in the enteric system. When colonic toxemia is proved in persons with normal bowel walls we shall accept it. Meanwhile we shall wonder about it and I shall be unable to explain why so many of my arthritics obtain subjective improvement from purgatives. I'm not certain that we know the whole story of colonic intoxication.

Into my office one day in September of last year came a patient who said that he was bothered with looseness of his bowels at times, particularly when he was fatigued. In November of 1935 he had gone to Puerto Rico by plane and the ship stopped over night at a small town in Cuba. There he drank water with the food served at a country hotel. About thirty-six hours later he began to have diarrhea. This continued without fever but with mucus in the stool for two months. There were mild cramping pains in his abdomen over that eight-week period and almost daily he would feel that he had to pass flatus and he would involuntarily pass a little bloody mucus onto his underwear. He wrote his family that he had acquired dysentery but he consulted no doctor about it. After the first two months he found that he was better in that he no longer soiled his clothing and he had only a very little blood and mucus in his stool. However, he did have from 3 to 6 loose movements of the bowels on most days and this condition obtained when I saw him. His physical examination revealed nothing remarkable; he had lost no weight. His stool was mushy and it contained a moderate amount of mucus and some flecks of blood. No motile amebae or cysts were found in it. Through the sigmoidoscope the rectal mucosa was hyperemic and edematous and it bled very easily when it was touched lightly with the tip of the instrument. Stool cultures showed *Bacillus dysenteriae* of the Flexner type. The blood serum in high titer agglutinated the Flexner bacilli. The diagnosis was clearly chronic bacillary dysentery and this case introduces us to the field of the ulcerative colitides.

## ULCERATIVE COLITIS

It is our custom to examine all patients who have bowel symptoms with the sigmoidoscope. We want to know the appearance of the colonic mucosa in patients with diarrhea and we note the state of the hemorrhoidal veins in constipated persons. In our hands sigmoidoscopy is a thoroughly medical procedure. No operating room or aseptic technic is required and any internist with a gentle hand is qualified to examine the lower 12 inches of the colon through an endoscope. The mucosa of the normal bowel is easily recognized; it resembles the lining of the cheek. In the first stage of ulcerative colitis the mucosa is hyperemic and friable and superficial ulceration may be present. I do believe that at times in the mucous colitis that I have called neurogenic, particularly when it is of long standing, one may see a hyperemic and edematous mucosa, the patient may have a temperature of  $99^{\circ}$  to  $99.6^{\circ}$  F., and a few leukocytes may be found in the colonic exudate. This may be called "catarrhal colitis" and it seems possible that the normal bacterial inhabitants of the colon have acquired some virulence or, more likely, that the resistance of the intestinal wall may have been lowered (perhaps by local treatment). In these cases I tend to hold to the fundamental neurogenic etiology unless they are proved to be specific and, though I may be stubborn, I think that the infection is superimposed on a spastic colon. In the second stage of ulceration the lesions are better defined and the mucosa between the ulcers is thickened and is very friable. The ulcers may be pin-point in size or they may be larger. Frequently the bleeding so clouds the field that we remark that the colon resembles a section of raw beef. In the third stage the ulcerations have reached the submucosa and they are very deep. Tufts of hypertrophic mucosa are between them. I cannot tell from the gross appearance of the ulcers the difference between those of amebic dysentery, bacillary dysentery, and nonspecific ulcerative colitis. Sometime when you are in Washington and after you have visited the public buildings, called on your congressman, seen the recent acquisitions at the Corcoran and the Smithsonian, visit the Army Medical Museum that is adjacent to the Smithsonian. There are displayed excellent specimens of ulcerated colons.

Whenever the endoscopic picture suggests that we are looking at an ulcerative lesion or when there is a long history of chronic diarrhea, we obtain through the sigmoidoscope specimens of stool and of exudate for immediate microscopic examination. The diagnosis of amebic dysentery is usually so very simple that it is ruled out first. In cases with active diarrhea and bowel ulceration the vegetative forms of amebae are quite easily found in the mucous exudate. When colitis is present and trichomonads are found in the stools, one should search especially carefully for amebae. A warm stage is not necessary for the recognition of these protozoa if the material has been obtained through the sigmoidoscope in an adjoining room or if it has been selected from stools passed at the laboratory. I am not enough of a parasitologist to be certain of my differentiation between *Endamoeba histolytica*, *E. coli*, *E. nana*, etc. If there is colitis and amebae are found, I presume that they are of etiologic significance until antiamebic treatment fails to relieve the symptoms. Occasionally I send the stools to the parasitologists in the Johns Hopkins School of Hygiene; with their greater acquaintance with protozoa, they sometimes pick up parasites which I have missed. When the patient is having formed stools, vegetative forms of amebae are less easily found and a search for encysted forms is made. This is not difficult and we use the method of Craig.<sup>4</sup> A bit of stool the size of a pea is emulsified with water or with normal salt solution in a test tube and this is strained through 2 layers of cheesecloth into a centrifuge tube. The tube is filled with water or with salt solution and centrifugalized at moderate speed for a few minutes. A drop of the sediment is placed on a slide and a drop of 2 per cent iodine solution is mixed with it. After about three minutes the specimen is examined with the high-power objective on the microscopic stage. Cysts of *E. histolytica* appear as lemon-yellow disks about the size of the ordinary leukocyte (or perhaps a little larger) that one sees in the urine. The nuclei and the karyosome stand out as refractile bodies. The cysts may contain 1, 2, 3 or 4 nuclei if they are of the *histolytica* variety. Paulson of Baltimore usually cultures the exudate or stool on a special medium made of human serum, rice flour, and liver infusion agar and frequently after three or four days amebae can be cultivated.

We do not do this routinely, however, and we are content with the simple microscopic examination of the stool to rule out diarrhea of protozoan etiology. Complement fixation tests for the detection of amebic infection have been devised by Craig and others. These are still in the experimental stage and in Baltimore they have been quite unreliable. Paulson has sent approximately 20 sera to Dr. Arnold of the Department of Pathology of the University of Illinois for a complement fixation test with the latter's technic. The specimens were numbered and Paulson has told me that Arnold selected the patients who harbored *E. histolytica* with considerable accuracy.

If no amebae are found, cultures of the stools are made for the typhoid-dysentery group of organisms. If suspicious colonies are found, they are worked out for us by the bacteriologists. Agglutination tests are also run with the patient's serum on the Sonne, Shiga, and Flexner (W and Z) strains of dysentery organisms. Frequently the dysentery bacillus cannot be grown but the serum from the patient in high titer will agglutinate a certain strain of bacilli. When this occurs, it is presumed that the ulcerative colitis is a dysentery.

When there is colonic ulceration, when no amebae are to be found, when there is no evidence of bacillary dysentery, when a Frei test (which I will mention again later) is negative, and when there is a history of insidious onset, we diagnose nonspecific ulcerative colitis. This is variously termed "colitis gravis," "idiopathic ulcerative colitis," and "suppurative colitis."

I believe the etiology of idiopathic ulcerative colitis to be still unknown. Workers in England have felt that it was an aberrant form of bacillary dysentery. Virulent strains of *Bacillus coli* have been accused of producing it; so have *B. proteus*, *B. mucosus capsulatus*, and others. In 1924 and 1925 Dr. Bagen,<sup>5</sup> working under Rosenow in the Mayo Clinic, presented what he considered to be evidence in support of his belief that a diplococcus was the specific cause of the disease. In his first 2 papers he reported that 75 strains of diplococci had been isolated by him from cases of ulcerative colitis, but only 25 of these had been studied culturally. The others had been identified morphologically (a most unreliable way to identify a diplococcus isolated from the intestinal tract), or by

agglutinations (an especially unreliable manner where streptococci and enterococci are concerned because many of them agglutinate spontaneously). In 1927 Dr. Bargaen<sup>6</sup> reported that he had isolated the organism in 189 of 266 cases and 105 strains had been studied culturally. In 1924 and 1925 Dr. Bargaen said that his bacterium was an  $\alpha$ -zoned diplococcus and that it never fermented inulin and mannite. In 1927 he said, "Of 105 strains tested, 41 fermented mannite and 64 did not." In 1930 he reported that his diplococcus "does not usually ferment mannite but lacks the power to ferment inulin." Dr. Bargaen said that his organism was heat resistant. He sent a typical strain to Torrey of Cornell and there it was not heat resistant. This conflicting evidence suggests to any critical observer that more than one type of coccus was dealt with. Dr. Bargaen injected his diplococci into rabbits and reported that many of them showed colonic ulcerations following these injections. He reported as controls the work of Rosenow and others who worked independently of Bargaen on different problems and they did not use other organisms isolated from the colons of patients with ulcerative colitis. Workers at the Mayo Clinic were impressed by Bargaen's experiments and sera were prepared and vaccines made. These preparations became the basis for the treatment of idiopathic ulcerative colitis at Rochester. The clinical results were considered to be quite satisfactory and the number of ileostomies done there annually was markedly lowered.

In 1926 and 1927 Paulson<sup>7</sup> of Baltimore made a study of the bacteriology of the colon in patients with ulcerative colitis. He studied 14 cases. From 13 of them he isolated 10 types of streptococci—including Bargaen's diplococcus (Bargaen's original criteria were applied in the classification). From the fourteenth case he could isolate only *Bacillus coli*. No one type of streptococcus was found to be present in more than 3 cases and Bargaen's organism was isolated in 2 cases. Paulson injected 7 of the 10 types of streptococci (including in this 7 the 2 strains of Bargaen's organism) into the venous system of rabbits. Five of the strains (again including Bargaen's diplococcus) produced primary inflammatory changes in the colon of 45 per cent of the animals injected. Paulson found that 2 types of living streptococci and a killed  $\beta$  hemolytic

streptococcus isolated from cases who did not have ulcerative colitis gave lesions when injected intravenously which were similar to those produced by Bargaen's organism and the streptococci from ulcerated colons. A living strain of *B. coli* from a case of amebic dysentery gave ulceration of the colon. This evidence seemed to show that Bargaen's organism was not specific in the etiology of idiopathic ulcerative colitis. Paulson studied the flora of the human ileum. He found that gram-positive cocci were normal inhabitants there and he learned that Garrod had found that by giving laxatives to normal persons he could increase tremendously the number of cocci in the stool. Ergo, anyone with a diarrhea is entitled to show diplococci or streptococci in the feces. They are simply washed down from the small intestine. Paulson noted, as had Hurst, that in the bloody culture medium of an ulcerative colitis the growth of cocci is encouraged. Therefore, these organisms are increased in the stools of the patients who have nonspecific ulcerative colitis but they are not the primary etiologic factor.

The theory that ulcerative colitis is due to a vitamin deficiency is certainly not proved and I regret to say that I have nothing constructive to contribute toward the search for its true cause.

**Treatment.**—The treatment of amebic colitis is quite simple and it may be readily obtained from the textbooks. To the average case we give emetine, carbarsone and chiniofon (yatren) simultaneously. Emetine gives almost immediate relief from symptoms but, unfortunately, it does not attack the encysted forms of the parasite. We give it as emetine hydrochloride in doses of 64 mg. daily for from seven to ten days. Of course it is given hypodermically. Rarely the emetine will aggravate the colitis by its excretion through the bowel. Then the dosage is reduced or it is given up entirely in the cases which seem to have an idiosyncrasy for it. Carbarsone is probably our most valuable therapeutic agent in amebic colitis. It is given in doses of 0.5 Gm. daily for ten days. We also give 2 Gm. of chiniofon in 200 cc. of water every other day as a retention enema. On the alternate days an 0.5-Gm. capsule of the same drug is given twice a day. With this triple attack we feel that the patient has the maximum opportunity to be rid of his parasites. After ten days of treatment the

patient is dismissed for three or four weeks and, if the parasites are found in the stools at the end of that period, the treatment is repeated.

Acute bacillary dysentery is usually a self-limited disease. The chronic form is quite intractable and rarely is the so-called "specific serum" specific. It may be tried, however, together with the general measures for the treatment of idiopathic ulcerative colitis which I shall mention or with any others which may prove effective in your hands.

In the treatment of nonspecific ulcerative colitis two things are in our favor: the disease has spontaneous remissions and we can always have the surgeons come to our rescue with an ileostomy. It is my present belief that ileostomy should be deferred as long as we dare defer it and, perhaps, a little longer. If we can just get the patient to hold out with us long enough, a remission is very likely to come. I don't mean that ileostomy should be postponed until the patient is in extremis. However, it should be withheld until we are driven to it by a persistence of local and general symptoms in the face of all medical measures. A complicating arthritis or other metastatic infection, marked undernutrition, and sometimes chronicity of symptoms are indications for ileostomy. The principles of the medical treatment of these patients are very like those of the treatment of tuberculosis or of any chronic infection: the patients should be generally built up. Forced feeding of a soft or smooth diet with quantities of vitamin-containing foods, cod liver oil, rest, sunshine, an equable climate, *i. e.*, Florida or the Gulf States in the winter, are the general measures. Several times I have seen remissions produced by the intramuscular injection of increasing doses of horse serum. Perhaps Barger's serum acts as a nonspecific protein and so does good. Rarely are irrigations and enemata necessary. When they are used, I prefer tannic acid in warm water. Bismuth by mouth is comforting and helpful. Vaccines have never impressed me with their usefulness in this condition, though they may be tried. Transfusions may be necessary and they often help the patient to get into a remission. In England anti-dysenteric serum is given intravenously. If it does good, I think that it is because it is foreign protein. At this time I know of no single measure so helpful to the patients as the

general up-building program. Remissions may last for months or years and between them the patients may be symptom-free, though the sigmoidoscopic picture may be that of an edematous friable bowel mucosa.

### LYMPHOPATHIA VENEREA

Ten or twelve years ago I was taught that all strictures of the rectum that were not carcinomatous and that had not followed rectal surgery were of syphilitic etiology. Later my pathologist friends told me that syphilis of the rectum (other than chancre or the mucous patches of the secondary stage) had never been proved. Then I heard that tuberculosis and gonorrhea were etiologic possibilities in this condition. I am still told that these conditions do produce rectal stricture but I have never seen strictures that could be definitely attributed to them. The pathologic reports on excised bits of stricture have uniformly read "chronic inflammatory tissue." In the past seven or eight years considerable evidence has been produced to show that probably the commonest cause of noncarcinomatous stricture of the lower rectum is lymphopathia venerea. This is also called lymphogranuloma inguinale, climatic bubo, or the sixth venereal disease. This is an interesting entity and I wish to consider it only in its relationship to colonic conditions. This disease is caused by a filterable virus and it differs from simple granuloma inguinale in its clinical manifestations, in its failure to show Leishman-Donovan bodies, and in its lack of response to antimony therapy.

Formerly lymphopathia venerea was considered to be a tropical disease, though its venereal mode of transmission was recognized. It now seems to be quite widely disseminated and to be most frequently found in peoples who are sexually somewhat promiscuous. The colored races, therefore, seem to be quite susceptible.

The virus of the disease has a predilection for the lymphatic system and, whether it produces inguinal buboes or rectal stricture, depends on its path in the lymphatics. In the male a small herpetiform lesion appears on the penis from ten to twenty days after exposure; it is considered to be inconse-



quential and it soon disappears. In two or three weeks there is swelling of the inguinal glands on one or both sides and suppuration of them is very common. The lymphatic inflammation may persist for a very long time. This is usually the extent of clinical manifestations in the male and in him rectal stricture is relatively rare. In the female similar buboes may occur if the primary lesion is on the vulva. However, the primary sore is usually on the cervix or in the upper vagina and, because the lymphatic drainage of these parts is into the anorectal glands rather than into the inguinals, there is involvement of the perirectal lymphatics with chronic inflammation or a granuloma and, as fibrous tissue forms, there is a gradual stenosis of the rectum. As one recalls his cases of benign rectal stricture, he remembers that by far the greater number of them was in females. It is said that rectal stricture from this disease is produced in males only by direct inoculation of the virus into the rectum, *i. e.*, by sodomy. My own opinion of the few male patients in whom I have seen benign rectal strictures makes me believe that this conception of the mode of infection of the rectum in males is probably correct.

In 1925 Frei reported that an antigen for diagnostic skin testing could be obtained by aspirating pus from a bubo of a patient with the disease. The pus is diluted and heated and is injected intradermally in persons suspected of the disease. In the positive cases a local reaction similar to the tuberculin reaction is obtained after forty-eight hours. The area of redness should be at least 0.5 cm. in diameter. It is dissimilar to the tuberculin reaction in the small area of necrosis of the skin at the center of the reaction. Virus which has been grown on artificial media may also be used for the test. Most workers with the test of Frei believe it to be practically specific for the infection. It is with this test that most cases of lymphogranuloma inguinale and rectal strictures caused by that disease are diagnosed. The test is positive for many years after the primary inoculation.

It has been my experience that most of the patients with nonmalignant rectal stricture have had rectal ulceration and diarrhea. Others have noted the ulceration above the stricture and they have discussed the cause of this. Some have felt

that the ulceration was due to the virus and others have felt that it was caused by fecal stasis. Recently the virus has been isolated from ulcerated colons above the strictures and positive Frei tests have been secured with that virus in known cases of lymphopathia venerea. The disease has been reproduced by the inoculation of virus obtained from an ulcerated bowel into the penis of a man who later gave a positive Frei test. Goodman<sup>8</sup> of the Section on Syphilis at the Johns Hopkins Hospital reported positive Frei tests in 7 patients from a series of 20 unselected cases of ulcerative proctitis and colitis without rectal strictures. He feels that lymphopathia venerea should be considered in the differential diagnosis of all cases of ulcerative colitis. Certainly it may produce a proctitis and Goodman believes that he has seen it produce ulceration of the entire colon and of the lower ileum.

**Treatment.**—The treatment of lymphopathia venerea is most unsatisfactory. Antimony does no good and we have left only the general measures used in nonspecific ulcerative colitis. Time is sometimes kind to these patients and in those with persistent trouble and marked rectal stricture we advise colostomy.

In the medical treatment of colonic conditions, especially in the treatment of the chronic ones, the well-known art of medical practice is invaluable. First, it keeps the patient sticking to the principles of his treatment by means of encouragement and hope; and, in the second place, it lends the ever necessary patience and the always helpful "will to get well."

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## CLINIC OF DR. W. S. TILLET

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#### THE SERUM TREATMENT OF PNEUMONIA

THE increasing use of type-specific antipneumococcus serum in the treatment of pneumonia indicates the growing recognition of its value as a therapeutic measure. In the past, a number of accessory factors pertaining to its practical use have retarded its general adoption by physicians even though large clinics have, for several years, found the treatment to be of definite value. At the present time, the continued simplification of procedures, both in the laboratory and at the bedside, is eliminating difficulties to such an extent that the successful administration of serum treatment is becoming increasingly more feasible. I should like to discuss certain points concerning serum treatment of pneumonia and to emphasize particularly the problems that need to be taken into consideration when apparently unsatisfactory results are obtained.

A large volume of literature has accumulated on the subject of serum therapy in pneumonia since the monograph of Avery, Chickering, Cole, and Dochez<sup>1</sup> appeared in 1917. Without reviewing in detail these reports, experience so far has shown that cases of type I pneumococcus pneumonia treated with the homologous antipneumococcus serum respond most satisfactorily. However, with a growing understanding of the immunologic background on which serum treatment is based, wider application may be reasonably expected. In addition to type I pneumococcus infections, 5 of the other specific types—II, V, VII, VIII, and XIV—have, up to the present time, been reported as being favorably influenced by appropriate specific anti-sera. The principles underlying treatment and the problems which may arise during treatment appear to be essentially

the same, regardless of the particular type of pneumococcus causing the infection. Consequently, this discussion is generally applicable, although only the treatment of type I pneumococcus pneumonia is taken up in detail.

In the administration of serum it is generally agreed that there are 3 requisites which promote the most favorable results. They are as follows:

**1. Treatment Begins within the First Twenty-four to Forty-eight Hours after Onset.**—Cecil<sup>2</sup> has recently summarized the results of early treatment and shows that in type I pneumococcus pneumonia the mortality of cases treated in first twenty-four hours of the disease is approximately 5 per cent, a mortality rate which he estimates to be about one sixth of the usual expectancy in cases not treated with serum.

In order to take advantage of the important factor of time, rapid determination of type of pneumococcus causing infection is necessary. Fortunately, the so-called "Quellungsreaktion," by which typing may be done on satisfactory specimens of sputum directly and within a few minutes, permits the laboratory to fulfil its duty with considerable accuracy and speed. The typing phenomenon consists of a swelling of the capsule on the pneumococci in the presence of homologous type-specific antibodies. It was first noted by Neufeld,<sup>3</sup> was more recently described by English investigators,<sup>4, 5</sup> and is well described in American literature.<sup>6, 7</sup> Experience of the past few years has shown that the test is a practical measure which is being generally adopted and that its use greatly increases the opportunity for physicians to begin treatment within a few hours or less of the time sputum is delivered to the laboratory for examination. The first condition, therefore, for best therapeutic results receives valuable aid from these more recent laboratory developments.

**2. The Amount of Serum per Dose Should be Adequate.**—The answer to this question cannot be given categorically but the experience of different clinics indicates fairly definitely the amounts which appear to be necessary. The removal of antibodies from whole serum and their concentration in small total quantities of fluid has facilitated greatly practical administration. The adoption of a unit for measurement of protective power of sera has also contributed to

standardizing dosage, which is regularly expressed in units per dose. The average initial dose is from 20,000 to 60,000 units at the Johns Hopkins Hospital, usually being 40,000. One may be guided to some extent by the severity of the case when first seen, the larger doses going to those patients who appear to be severely ill and who may have a septicemia. As a general rule, it is perhaps desirable to lean to the side of the larger dosage since adequate amounts are of great importance and since the liability to reaction is not seriously increased.

### 3. The Repetition of Injections is Also Important.—

As the serum treatment of pneumonia has been improved it is interesting to note that the interval of time between treatments has been continually shortened. At the present time the opinion seems to prevail that the second treatment should be given not longer than four hours after the first; even two hours is preferable, providing the immediate reaction of the patient—if any has occurred—to the first injection has not been unusually marked, and has subsided. The dosage for the second treatment may be 20,000 to 40,000 units, preferably the latter. A third treatment is usually desirable, using the same interval and the same dosage as in the second injection. Following this régime it may be seen that in from four to eight hours after beginning treatment, patients will have received from 60,000 to 120,000 units.

In patients treated early in the disease and in the manner described it is the rule to see great improvement and even recovery in twenty-four to forty-eight hours; whether or not additional treatment is indicated depends on the individual case. In severe illnesses with septicemia continuation of intensive treatment is indicated and the results often justify the efforts.

Several methods have been devised as guides to both dosage and duration of serum treatment. One of these consists of testing samples of serum from the patient at intervals for the presence of excess circulating antibodies. Another method consists of skin tests with the type-specific polysaccharides. A positive test occurs as a wheal in fifteen to thirty minutes and is intimately associated with a favorable prognosis. For details concerning these procedures, you may refer to detailed reports in the literature.<sup>2, 7</sup>

It is not possible at this time to discuss in detail all the measures which come up for consideration in serum treatment. Brief mention may be made, however, of the following: (a) test before injections, for patient's possible sensitivity to serum; (b) slow introduction of serum, particularly the initial injection; (c) dilution (1-5 times) of serum with physiologic salt solution if patient is desperately ill or if unusual reaction may be suspected from history of patient.

It should also be emphasized that although best results are obtained with patients treated early, favorable results are also obtained in cases treated later in the disease. Although statistical evidence in large series may not give striking proof of the value of serum in patients treated late after onset, there are a sufficient number of individual instances, in which patients severely ill after several days of pneumonia were definitely benefited by serum. Its use should therefore be seriously considered in any case with well-marked active infection regardless of the time in the course of the disease at which the patient first comes under observations.

Of particular interest are patients, not infrequently encountered, who do not respond satisfactorily, even though the serum therapy was properly administered. The patient to be described will serve as a basis for a discussion of some of the reasons for unsuccessful serum results.

Patient B. F., thirty-one-year-old housewife, was admitted on the third day after cough and fever had developed, following a "cold" of ten days' duration. She did not at first appear acutely toxic although respirations were rapid and labored. She presented classical signs of consolidation of left lower lobe. Correct typing was unfortunately not obtained for eighteen hours. It finally proved to be type I pneumococcus. Blood culture was positive, with 38 colonies per cubic centimeter. White blood corpuscles 12,200 per cubic centimeter at time of admission. She received a total of 220,000 units of type I antipneumococcus serum in approximately thirty hours. A second blood culture taken on day following beginning of treatment was sterile. On the day after admission there was evidence of spread of the lesion and x-ray suggested fluid at left base. Attempts to find fluid by thoracentesis were not successful. Patient died six days after admission on ninth day of disease. At autopsy pneumonia was present and also encapsulated empyemata on both sides close to mediastinum.

In this patient it is difficult to assess the importance of the pleural infection *per se* since she had considerable general in-



fection at the time of admission. Through vigorous serum treatment it was possible to sterilize the blood stream but the severity of the infection from all points of view was too great to be overcome. The course of this patient serves, however, to illustrate the fact that complications of pneumonia, such as empyema, may appear which confuse the picture. Because empyema is relatively so common in pneumonia, its possible presence should be suspected *first* in patients who ought to respond to treatment but who remain acutely ill. In other patients whose condition may be complicated by empyema the pleural infection may appear later in the course of the pneumonia than in the patient just described, and as a result prolong the illness beyond the time of expected recovery. If the pus in the pleural cavity is located next to the thoracic wall instead of adjacent to the mediastinum the condition is not difficult to diagnose or treat successfully by appropriate drainage. While considering the subject of empyema, it is also important to bear in mind that this complication is more likely to occur in patients with type I pneumonia than in the other types, whether serum treatment is used or not.

Other complications, which require special measures and are not combated successfully by serum alone, may also intervene. They may be part of the pneumococcus infection itself, as, for example, meningitis or pericarditis. They may be dependent upon a superimposed complication due to some other organism, such as streptococcus or staphylococcus. Several other complicating manifestations might be mentioned, such as lung abscess or phlebitis. However, it is easy to see, from those described, how important it is to assay carefully the possible causes for continuation of acute illness in patients who receive serum.

There are other conditioning factors which should be given consideration when serum therapy is ineffective. For example, a mistake in typing may be made by the laboratory. This error is part of the human equation and inevitably occurs. When, therefore, in the absence of demonstrable complications and in spite of adequate treatment, the course of the disease is not influenced, a careful recheck of sputum typing should be requested.

Analyzing further the instances of poor results, the failure

of serum to be helpful may be accounted for by imperfections in the patients' reaction to the infection. For example, a leukopenia may be present. Since the mechanism of the curative action of serum is opsonization of the organisms, phagocytosis is necessary to complete the eradication of the pneumococci. Insufficient numbers of leukocytes may therefore delay the process. When this occurs, blood transfusions are sometimes helpful.

In still other patients, the failure of some element of their own mechanism of defense seems to occur, but no method of measuring the deficiency has, as yet, been devised. Because of our ignorance in this respect, no forms of supportive treatment have been found to be uniformly helpful. The need for additional study in this group of patients is obvious.

With respect to the treatment of pneumonia due to types of pneumococci other than type I—namely II, V, VII, VIII, and XIV—experience with type II has been the largest. The results have been less impressive than those obtained in type I cases. However, they indicate that if treatment is started early and if dosage of serum is large, perhaps 40,000 to 80,000 units per dose and with an average total of 150,000 to 200,000 units, the results are definitely favorable. Bullowa,<sup>8</sup> Finland and Tilghman and their associates,<sup>9</sup> have presented their results concerning types V and VII. From their reports, as well as from the limited experience here, the outlook is promising that these types of infection may be benefited by homologous type-specific serum and that their regular use is indicated. Bullowa has also related his experience with serum in the treatment of cases of type VIII pneumococcus pneumonia,<sup>10</sup> and also of type XIV.<sup>11</sup> He reports favorable results in both instances. Viewing the continuing development of the serum treatment of pneumonia it seems likely that as the immunologic background is more completely understood the application of the principles to patients will become more useful and more practical.

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## CLINIC OF DR. MOSES PAULSON

### THE JOHNS HOPKINS HOSPITAL

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#### NEWER ASPECTS OF GALLBLADDER DISEASE OF PRACTICAL IMPORT

*The Problem—Physiology and Pathologic Physiology of the Extrahepatic Biliary System—Differential Diagnoses and Methods—Final Disposition: Selection of Cases for Surgical Intervention and for Medical Management—Medical Management: Dieto-Pharmaco and Psychotherapies*

**The Problem.**—Gallbladder operations frequently do not give the anticipated relief from symptoms for which they were performed. For years, some internists, like my Chief, Thomas R. Brown, and my colleague, John Tilden Howard, have made such a claim to which little attention was paid. Of late, first-rate surgical clinics are reporting that about 33 $\frac{1}{3}$  to 43 per cent of those so submitted have felt that little or no benefit was derived therefrom. Thus, it becomes desirable to examine the several practical considerations toward facilitating and improving diagnosis and toward a more critical selection of cases both for medical and for surgical therapy.

In most situations, the principle holds that disease should be attacked early to secure the best therapeutic results. This was suggested for cholecystitis by Alvarez in 1923. However, today there is reason to believe that this principle does not hold in biliary tract disease. For instance, when comparisons are made of the results of gallbladder surgery in cases with minimal changes to those in whom the changes were more advanced, the inescapable conclusion—from a statistical standpoint—is that cholecystectomy should not be undertaken in early cases before marked changes occur. This is not to be carried to its logical conclusion; the problem is not quite so simple, since too long-standing involvements result in irreparable damage to the liver, pancreas and extrahepatic bile ducts.

Thus, to the family practitioner to whom the vast majority of these cases come for diagnosis and relief, and into whose hands is placed their disposition, the following questions must arise in instances where gallbladder disease is suspected.

1. How much does the gallbladder contribute to the patient's complaints?

2. How shall the diagnosis be established?

3. What cases shall be treated medically?

4. Who shall be submitted to surgery?

5. What shall be the procedure in the face of recurring preoperative or new postoperative symptoms; what are their causes and what is to be done for them?

**Applied Physiology of the Extrahepatic Biliary Tract.**—A step toward answering these questions will be taken upon the pointing out of the few known practical facts of extrahepatic biliary tract function. The gallbladder, like the intestine, manifests three types of activity: (1) absorption, (2) secretion, and (3) motor activity.

1. *Absorption.*—Hepatic bile is concentrated in the normal gallbladder four to ten times and is slightly acidified on reaching the unimpaired viscus, thus rendering fats and cholesterol soluble. An acutely inflamed mucosa will not concentrate bile. If such inflammation is patchy, it may do so to a varying extent. Degrees of partial bile concentration also occur when only the muscularis or serosa is involved. Upon recovery, if there is not too much replacement by fibrosis, the organ may again adequately concentrate. The gallbladder mucosa may become hypertrophied, either because of long-standing disturbances of duodenal motility or a hypertonic sphincter of Oddi. Nevertheless, concentration occurs here. Papillomata seem not to influence this function.

2. *Secretion.*—It has been noted by Ivy and his co-workers that in a dog with a gallbladder fistula and cystic duct obstruction, about 20 cc. of a mucoid fluid is secreted in twenty-four hours. The ducts secrete a slight viscous substance. In common duct obstruction, green fluid is noted with a relatively normal gallbladder, and "white bile" is a result of concomitant gallbladder disease or absence of the organ, and is associated usually with a hepatitis.

3. *Motor Activity.*—Ivy has shown that a hormone found

in the duodenum, which he has designated as cholecystokinin, is the chief stimulus to gallbladder contraction. Acids and fats are excitants to this hormone. Of such practical excitants, egg yolk and cream are the most effective. Atropine relaxes and morphine increases gallbladder tone, while pituitary solution causes some expulsion of bile, but these do not abolish the action of cholecystokinin.

The contraction of the gallbladder depends on three factors: the tone of the duodenum, the tone of the sphincter of Oddi, and the resistance of the flow of bile from the common duct into the duodenum. The functions of the sphincter of Oddi relate to the filling and emptying of the gallbladder as well as to the prevention both of the regurgitation of bile and the transmission of pressure from the duodenum to the common bile duct. Thus when the sphincter contracts, the gallbladder relaxes and fills and when the sphincter relaxes, the gallbladder contracts and expels its contents. This relationship is further seen in the sphincter becoming incompetent when the gallbladder is removed, but later its competency is recovered and the ducts dilate.

Any increase in duodenal tone may delay as well as any decrease in tone may increase the gallbladder evacuation. Atropine decreases and morphine increases such duodenal tone. The sphincter of Oddi can resist up to 75 cm. of bile pressure, whereas the maximum expulsion of the gallbladder is 30 cm. of bile pressure. Therefore, a spastic sphincter can resist gallbladder evacuation.

Three pathologic-physiologic processes may follow from a disturbed sphincter of Oddi-gallbladder relationship:

1. Increased activity both of the gallbladder and the ampulla with rapid emptying. This is known as the hyperkinetic type of evacuation.

2. Contraction of the gallbladder against spasm of the sphincter resulting in biliary colic and called "hypertonic dyskinesia."

3. An atonic gallbladder in consequence of a spastic sphincter with a resulting heavy, aching sensation.

Let us now revert to several of the questions asked at the outset. How much does the gallbladder contribute to the

complaints? How shall the diagnosis be established? Who shall be treated medically and who surgically?

**The Differential Diagnosis.**—If one suffers with frequent attacks of colic caused by calculi, the removal is indicated and the results are striking. On the other hand, little relief can be expected of surgery from mild symptoms—often due to other conditions—and mild gallbladder changes. Here there can be no real consolation that the excised gallbladder showed some alteration. Not only is there no agreement among pathologists as to what is a normal gallbladder, but rarely is a gallbladder pronounced normal on the basis of microscopy.

The problem becomes relatively easy when the following are obtained: (1) a satisfactory account or evidence of one or more attacks of biliary colic, with or without fever, chills and jaundice; (2) residual tenderness following such painful episodes; (3) possibly indigestion between attacks, characterized by flatulence, bloating and discomfort. However, if diagnosis is to be improved, if a better selection of cases for medical and for surgical therapy is to be made, the possible presence of any one of several other conditions, or a combination of them resulting in similar, if not in identical complaints,

TABLE 1

IMPORTANCE OF PATHOLOGIC CHANGES TO PROGNOSIS AFTER CHOLECYSTECTOMY\*

	Well.	Im- proved.	Unim- proved.	Postop- erative death.	Total.
Minimal lesion.....	11	22	21	3	57
Cholesterosis.....	14	2	14	1	31
Chronic catarrhal cholecystitis...	18	16	13	4	51
Chronic fibrous cholecystitis....	2	3	0	0	5
Cholesterosis with stone.....	6	11	0	0	17
	51 or 54, or 31.7% 33.5%				161

\* From Graham E. A., and Mackey, W. A.: Jour. Amer. Med. Assoc., 103: 1497-1499 (Nov. 17), 1934.



TABLE 2

THE PRESENCE OR ABSENCE OF CHOLELITHIASIS AND RESULTS\* †

	Cases.	Hospital mortality.	Follow-up.	Symptomatic results.	
				Satisfactory.	Unsatisfactory.
Stone present...	423	15 3.5%	308	243 79.0%	65 21.0%
Stone absent....	187	7 3.7%	139	89 64.0%	50 36.0%
Total.....	610	22	447	332	115

\* Statistical evaluation applied to operative mortality:  $P = 0.91$ ; not significant. Statistical evaluation applied to symptomatic results:  $P = 0.01$  —; significant.

† From Wilson, W. D., Lehman, E. P., and Goodwin, W. H.: Jour. Amer. Med. Assoc., 106: 2209-2213 (June 27), 1936.

TABLE 3

DEGREE OF PATHOLOGIC CHANGE AND RESULTS\*

	Cases.	Follow-up.	Symptomatic results.	
			Satisfactory.	Unsatisfactory.
With and without stone:				
Mild . . .	104	86	49 57.0%	37 43.0%
Moderate . . . .	359	248	190 76.6%	58 23.4%
Marked . . . .	147	113	93 82.2%	20 17.8%
Total . . . . .	610	447	332	115

Note. Degrees of pathologic change "with stone" and "without stone" not shown because symptomatic results were not statistically significant.

\* From Wilson, W. D., Lehman, E. P., and Goodwin, W. H.: Jour. Amer. Med. Assoc., 106: 2209-2213 (June 27), 1936.

must be more readily recognized. Thus, gallbladder colic may be mimicked by tabes dorsalis, perforating peptic ulcer, renal calculi, hydronephrosis, root pains of spinal and vertebral lesions. It will be important to know whether the colic is due to stone or to the already referred to pathologic-physiologic state of the contraction of the gallbladder against a spastic sphincter of Oddi, designated as hypertonic dyskinesia.

The jaundice suspected of being obstructive may be intra-hepatic, or hemolytic, or may be manifestations of familial or congenital hyperbilirubinemia, pernicious anemia or carotinemia.

How are these conditions to be differentiated? In many instances, the mere thinking of these possibilities plus adequate history taking—the most important single method of diagnosis—will go a long way toward clarification. In addition to a satisfactory physical examination, it will be necessary to resort to simple laboratory procedures, many of which the progressive practitioner will be able to do for himself.

Satisfactory evidence of lues and the nature and extent of therapy, Wassermann reactions on blood and spinal fluid, should solve the question of tabes. Plain plates of the abdomen will reveal radiable biliary, renal, ureteral or urinary-vesicle calculi, vertebral lesions, as well as subdiaphragmatic gas as seen in perforated peptic ulcer. Intravenous urography, now a relatively simple procedure, the application of which is not contraindicated in jaundice, will furnish additional data of a positive or negative nature, either of which are obviously important in differential diagnosis. The rare instance of jaundice of pernicious anemia will be recognized by an adequate blood study which should be part of the routine of a complete examination. Carotinemia may be suggested by the history. It can be eliminated readily as follows:

Add an equal part of chemically pure acetone to the serum to be used in determining the icteric index. The mixture, then, is centrifuged, and carotin as well as hemolyzed red blood corpuscles and proteins are precipitated. The intensity of the supernatant fluid of clear, yellow serum is tested against known icteric index standards. The result is multiplied by two because of acetone dilution. This sum represents the extent of serum bilirubinemia and establishes the true icteric index.

Hemolytic jaundice, particularly the typical type, is readily recognizable. Unlike obstructive jaundice, it is chronic, of long duration, is relatively mild, presents a variable but persistent slight jaundice, and manifests splenomegaly. The essential laboratory data reveal fragility changes and spherical microcytes in the peripheral blood, the latter being regarded by William P. Thompson as pathognomonic of the disease. The van den Bergh reaction is indirect. Since many with hemolytic jaundice eventually develop biliary calculi, both hemolytic and obstructive jaundice may be present simultaneously.

The common and more difficult differential diagnostic problem is that of intrahepatic from extrahepatic jaundice. The former is not always painless and the latter is not always strikingly painful. The distinction is important since intrahepatic jaundice is a medical problem and extrahepatic jaundice may necessitate surgery. The solution can be aided greatly by the proper application of the galactose tolerance test shortly after the onset of jaundice. This method is based on the facts that galactose is practically unutilizable by any structure other than the liver, that there is no renal threshold for the excretion of this carbohydrate, and, unlike glucose, galactose is unmodified by the activity of the endocrine glands. Thus, in the sudden hepatic involvement of intrahepatic jaundice, before there is time for ample hepatic regeneration, excessive galactose is excreted in the urine. Following an overnight fast without any other food, galactose totaling 3 Gm. or more in urine collected at five consecutive hourly intervals subsequent to the ingestion of 40 Gm. of galactose, is indicative of hepatic damage as being the cause of jaundice. The negative finding will not be significant unless the test is done early in the course of the disease, since a day or two may be sufficient, in some cases, to allow the liver to compensate. The technic is very simple; any practitioner equipped to do Benedict's or Fehling's qualitative and quantitative reactions will be able to perform this test. Those interested are referred for further details, which space does not permit to present here, to the articles of Shay and his co-workers, to whom great credit is due for reviving, modifying and stimulating interest in this important differential diagnostic method.

The teaching has been that relatively long-standing bloat-

ing, fulness, flatulence, indefinite dyspepsia or poorly localized attacks of abdominal pain, with or without nausea and emesis, particularly if they occur in women who have been pregnant and especially if they are overweight, are likely to be due to gallbladder disease. Since the advent of cholecystography, the diagnosis appeared more certain to some, if the x-ray were in any wise suggestive of disease. This teaching seems to be in need of revision. It is not believed that many with only such symptomatology can be said to have it as a result of gallbladder affection, even if there be evidence of some pathology in that organ. It must be remembered that coincidental occurrences—pathology and symptoms—do not always indicate a cause and effect relationship. Besides, the more recent evidence from first-rate surgical clinics points out that removal of the assumed cause—the gallbladder—does not bring anticipated relief in this type of case sufficiently often.

If not the gallbladder, what, then, may account for such difficulties? Atypical manifestations of peptic ulcer, small intestinal deviations, and renal lesions reflexly, often give rise to similar complaints. The same symptoms—sometimes designated as gallbladder dyspepsia—will also be found in some with low basal metabolic rates, in chronic nervous exhaustion with or without demonstrable changes in tone and/or secretion of the digestive apparatus, in constitutional inadequacies with and without affective disorders in the irritable colon, and in some with any change in digestive function on a psychogenic or neurogenic basis.

First thinking of, and then directing the history into the channels of such possibilities, will go far toward untying the knot. Thus, queries indicating unusual sensitiveness to cold, usually but not always with easy fatigue, should suggest the possibility of a low basal metabolic rate. And answers to such simple questions as, "Do you think the world is treating you right?" "Are you sad?" "Do you sleep well?" will often be found to be the first steps toward revealing temperament, depression, attitude, hopes, anxieties and destroyed ambitions, maladjustments and other psychogenic factors at play. To pay attention to this phase only after organic disease has been eliminated is an error, for often psychogenic and organic disturbances are concomitantly present, and complaints actually

flowing from the former are erroneously attributed to the symptomless structural changes. The rôle of pathologic physiology, not due to structural defect, in the production of symptoms, has been too long neglected under the influence of the German school of pathologic anatomy and the rapid progress of laboratory medicine.

It has been pointed out that the greatest benefits from surgery are restricted to those who have had biliary colic due to stone and in whom the gallbladder involvement is not mild. How is one to ascertain the extent of pathology and the presence of stones? Two valuable laboratory adjuncts are available: the nonsurgical biliary drainage of Lyon, and cholecystography. *x*-Rays may be corroboratory but will not add much information to those experienced with the former. Bockus, Shay, Willard and Pessel have demonstrated that cholesterol crystals and calcium bilirubinate in duodenal aspirates ("B" bile) are pathognomonic and cholesterol crystals highly suggestive of stone, while many white blood corpuscles indicate infection. Cholecystography is more widely used and

TABLE 4  
CHOLECYSTOGRAM AND PATHOLOGIC CHANGE\*

Degree of pathologic change.	Normal shadow.	Good shadow.	Poor shadow.	No shadow.	
With stone:					
Mild.. . . .	3	4	0	1	
Moderate	2	7	25	76	
Marked	0	0	10	30	
Total	5	11	35	107	158
With and without stone:					
Mild	14	16	17	12	
Moderate	6	12	38	93	
Marked	0	0	12	32	
Total	20	28	67	137	252

Note: The part of the table concerning "without stone" has been eliminated because the results were not statistically significant.

\* From Wilson, W. D., Lehman, E. P., and Goodwin, W. H.: Jour. Amer. Med. Assoc. 105: 2209-2213 (June 27), 1936.

is very helpful. Its careful application gives results upon which anatomic-pathologic change in the gallbladder as well as functional alterations may be detected. In studying the accuracy of cholecystography in determining cholelithiasis, Case found stones in 95.7 per cent of cases where the report was either "no shadow" or "stone positive." Cholecystography, when considered with a good history, has been found accurate in 90 to 95 per cent of cases by Palmer and Ferguson. On the other hand, where the gallbladder was removed in the face of normal or good cholecystographic shadows, 50 per cent of the results were said to be poor. It is conceivable that some of the 50 per cent of good results may be due to psychotherapy brought about by surgery; this will be referred to shortly.

**Therapy.**—*Prophylaxis.*—Little is known concerning this. Ivy suggests the adequate daily intake of fat to evacuate the gallbladder as a phase of antepartum care and in the atonic symptomless gallbladder.

*Cases selected for surgery* should be limited to those who present stones, relatively advanced gallbladder changes and in whom there is evidence of *more than one attack of biliary colic*. To establish the last is important for two reasons: (1) Blackford, King and Sherwood in following 100 cases of biliary colic found no recurrences of colic in 40 per cent of patients after the initial examination. (2) Maynard reports that in 223 cholecystectomies, 24 gallbladders were found to be normal. Seventy per cent of the latter's possessors regarded their operations as successful, a psychotherapeutic effect achievable by less drastic means.

*Cases Selected for Medical Management.*—These should consist of all of those who fail to meet the criteria for surgical intervention.

*Dietotherapy.*—In acute gallbladder disease, fat and fruit juices are interdicted. The former may result in the contraction of an organ requiring rest, and the latter may unduly chemically stimulate a concomitantly disturbed digestive tract. In the chronic disorders, individual tolerance to these foods must be ascertained. In general, a well-balanced dietary in which the physical, chemical and mechanical factors are reduced (smooth diet) will suffice.

*Pharmacotherapy.*—It is believed that the dyspeptic manifestations ascribed to gallbladder disease, are—in many instances—due to an irritable digestive apparatus. Magnesium sulfate, intended to relax the sphincter of Oddi and to stimulate bile flow, and the various bile salt preparations, most of which contain either calomel, cascara or phenolphthalein, eventually become intestinal irritants and exaggerate both the dysfunction and symptoms. Atropine and its derivatives, sedation, and oil by mouth and by rectum are helpful.

*Psychotherapy.*—Finally, the patient is to be assured that the extent of the disease bears little or no relation to his complaints, and that the prognosis is good. Further, he is to be shown how his temperament as the soil, and his responses to his problems and environment as the seeds, bring forth the flower of pathological physiology accountable for his complaints. Adjustment of the intelligent patient to whatever complaints arise or continue on this basis will often follow.

*Involvements Following Surgery for Cholecystic Disease.*—Following surgery, the recurrence of three symptoms should excite immediate attention. These are pain, jaundice and possibly dyspepsia. There are three causes for this: (1) an hepatitis which may arise from the gallbladder infection, carried by the lymphatics, or from an ascending cholangitis. This can be determined early by a serum bilirubinemia, a direct van den Bergh reaction, and the retention of bromsulfalein weeks to months after surgery. Here it is hoped that the condition will subside spontaneously. (2) A stricture or stone in the common duct presents, in addition to jaundice and colic, chills and fever and is in need of surgical intervention to prevent an ascending cholangitis with biliary cirrhosis, splenic enlargement and finally hepatic insufficiency. (3) The more common postcholecystectomy distress is seen not infrequently shortly after operations, and sometimes later. The early episodes may be associated with the passing of mucus and debris, or with slowly regressing inflammation; the later attacks may be concerned with dilatation of the ducts and spasm of sphincter of Oddi. Here the medical management is not unlike that already suggested for nonsurgical gallbladder disease and simulating disturbances.

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### FACTORS OF INTEREST IN THE DIAGNOSIS OF LIVER DISEASE

THE liver is the largest of the glandular structures; it is the center of many metabolic activities and in its relation to the portal circulation it occupies a strategic position between the gastro-intestinal tract and the rest of the body. One might expect it to be vulnerable. Although there are indications of minor disturbances of the liver in many generalized diseased states, particularly in those associated with fever and with anoxemia, major diseases of the liver are comparatively rare. This relative rarity would be surprising were we not so imbued with the idea of this organ's unusual reserve power and its remarkable regenerative capacity.

It has been pointed out many times that the most obvious clinical manifestations of liver disease have to do with the excretion of bile, with its relation to the portal circulation and with its variability in size. Our chief reliance in hepatic diagnosis must rest upon careful history taking and the usual bedside methods of observation and physical examination with particular emphasis upon the three fundamental factors just mentioned or the corresponding pathologic phenomena of jaundice, portal obstruction and enlargement or shrinkage of the liver. This method of approach often suffices but in the difficulties of differential diagnosis that may arise reliable tests of the functional capacity of the liver become highly desirable. It is obvious that with an organ of such multiplicity of function, no single all-embracing test need be expected. Many methods have been devised to test each of the known functions

of the liver and a few of them seem to many observers to be helpful under certain conditions. No attempt will be made to list these tests but after a consideration of the fundamental clinical factors we may consider briefly some of the tests that have come to be a part of the clinical armamentarium in many hospitals.

**Jaundice.**—Probably the most important clinical sign of liver disease is jaundice and the study of its pathogenesis has been most stimulating and instructive. Bilirubin derived from hemoglobin is brought in the circulation to the liver cells which excrete it along with other constituents of the bile into the bile canaliculi whence it passes down the bile passages into the intestines. Here the bilirubin is reduced to urobilin, a part of which is absorbed, carried back to the liver and again excreted into the bile. When the excretory function of the liver is depressed, the urobilin may accumulate to some extent in the blood stream and be excreted by the kidneys into the urine. Urobilinuria is hence regarded as an indication of depressed activity on the part of the liver.

A useful concept emphasized by Rich<sup>1</sup> is the division of jaundice into two main types, retention jaundice and regurgitation jaundice.

In retention jaundice, the bilirubin circulating in the blood stream may not all be excreted by the liver cells and accumulates in the blood. Under these circumstances the bilirubin seems to be bound in some way, perhaps to the plasma proteins, gives an indirect van den Bergh reaction and does not pass through the kidneys into the urine (acholuric jaundice). A retention jaundice, associated with milder forms of liver injury, cloudy swelling or atrophy of cells, is due to an increased formation of bilirubin together with a depressed excretory function of the liver due in turn to different factors, particularly anoxemia, fever, and in the case of the newborn to immaturity of the liver cells. This milder type of jaundice and of liver injury is associated with such diseases as the hemolytic anemias, congestive heart failure, malaria and lobar pneumonia.

In regurgitation jaundice, on the other hand, the bilirubin is excreted by the liver cells and then escapes from the bile canaliculi into the tissue spaces and blood sinusoids of the

liver, either by reason of obstruction of the larger bile ducts or by necrosis of the liver cells. In this case, not only bilirubin but the whole bile gets into the blood stream. The bile pigment now is not bound, it gives a direct van den Bergh reaction and is readily excreted by the kidneys into the urine (choloric jaundice). This is the type of jaundice associated with the major liver disorders. The careful observation of the occurrence of bile pigments in the tissues, in the urine and in the intestinal tract, and laboratory studies of the qualitative and quantitative relationships of bilirubin in the blood are the most valuable diagnostic features in acute liver disease and may be useful also in chronic conditions.

**Portal Obstruction and Other Causes of Water Retention.**—Until recently it has been generally assumed that ascites in liver disease was due entirely to obstruction of the portal radicles within the liver and that the dependent edema sometimes noted was caused by the pressure of the ascitic fluid upon the vena cava. It is now realized that this does not account for all the water retention in liver disease.

The presence of ascites of even moderate degree is usually an obvious clinical finding. The swollen abdomen is in striking contrast to the pinched and emaciated appearance of the body elsewhere. In addition to the ascites or even in its absence one may find other evidence of portal obstruction in the development of collateral venous channels. Dilated veins may be readily visible on the thoracic and abdominal walls, dilatation of hemorrhoidal veins may be noted and by the use of a thick barium paste esophageal varices may be readily demonstrated by roentgenography. The presence of blood in the vomitus or in the stools may signal the presence of esophageal varices.

The occurrence of water retention in both acute and chronic liver disease in the absence of ascites has been noted by a number of observers. Jones<sup>2</sup> has emphasized the occurrence of a spontaneous diuresis at a certain stage in acute liver disease and inasmuch as this is followed usually by rapid clinical improvement he presents it as a valuable and favorable prognostic indication.

One probable cause of the disturbance in the fluid balance in liver disorders may be related to the blood plasma proteins.

Several observers<sup>3</sup> have noted some disturbance of the plasma proteins in all types of liver disease. This change is especially notable in chronic diffuse diseases of the liver (cirrhosis) where the total plasma proteins are reduced and particularly the albumin fraction. The globulin fraction may be less reduced or it may actually be increased with the result of an inversion of the albumin-globulin ratio. In the reports of several studies of this type the albumin of the blood plasma has been usually below 2.5 Gm. per 100 cc. in cases of cirrhosis. Several students of this problem believe that the hypo-albuminemia may itself be an indication of hepatic insufficiency. Myers and Keefer<sup>4</sup> were unable to increase the plasma proteins by high protein diet in their patients, hence the finding of low blood protein values does not seem to indicate the advisability of a high protein diet in therapy.

Changes in the size, shape and consistency of the liver are of value primarily in calling attention to a pathologic change in the organ and may also be of differential diagnostic significance. Very familiar to all of us is the uniformly enlarged and tender liver of chronic passive congestion. I may cite further the slightly to moderately enlarged and slightly tender liver in its acute diffuse disorders, the firm, easily palpable liver edge in cirrhosis, and the large, hard, and perhaps, irregular liver in neoplastic states. Observations of changes in size and in contour may be of great value in following individual cases. The originally enlarged liver in an acute diffuse disease may become gradually or rapidly smaller and its disappearance beneath the costal margin may accompany other distressing features of an acute yellow atrophy.

**Functional Tests of Hepatic Insufficiency.**<sup>5</sup>—In the search for aid in the study of liver diseases and in problems of differential diagnosis tests have been devised for the study of many of its functions including those having to do with the metabolism of carbohydrates, of proteins, and of fats, its detoxication power and its ability to excrete certain substances into the bile. Some of these tests have come into fairly general use and this may be taken perhaps, to some extent, as a measure of their helpfulness. In view of the great reserve power in all these functions the tests are of possible importance only when lesions are widespread or diffuse throughout the liver.

They are usually negative, for example, in such conditions as solitary abscess or sparsely scattered metastases in the organ.

In cases with jaundice the study of the bile pigments in the urine, in the stools, in the duodenal contents, and in the blood serum is distinctly helpful. The indirect and the direct reactions of the van den Bergh test for bilirubin in the blood serum distinguish between retention and regurgitation jaundice. The presence of a direct van den Bergh reaction may reveal the presence of a subclinical jaundice. By means of the quantitative van den Bergh or the simpler icterus index the amount of the bilirubin in the blood serum may be determined from time to time and its increase or decrease may be of considerable value in the observation of a puzzling case. In diffuse necrosis of the liver there is usually a steady increase in the serum bilirubin to a maximum and then with regeneration of cells a gradual fall in bilirubin values. In obstructive jaundice, on the other hand, there is a rise to a moderate level and then a sustained plateau with comparatively minor fluctuations in the values of serum bilirubin.

In cases without jaundice the study of the behavior of injected bilirubin indicates that this may prove to be a more delicate test than most others that have been devised. It will be noted that the substance used is one normally and constantly being excreted by the liver and its use as an excretory test is therefore quite rational. So far the expense of the pure bilirubin and the somewhat involved technic have militated against its general usefulness.

Other excretory tests are based upon the fact that several dyes (phenoltetrachlorophthalein, bromsulfalein, rose bengal) have been found that are excreted entirely or almost entirely into the bile. They are also recognized quantitatively when retained in the blood serum and are measured by colorimetric methods. These tests have become popular and are of particular value in the absence of jaundice or when the degree of jaundice is minimal. Obviously when there is marked jaundice the retention of the dye in the serum may merely parallel the degree of the jaundice. Sometimes there is found a marked disproportion of dye retention in cases of small degrees of jaundice. Probably the most widely used of these tests is the bromsulfalein test. In the performance of the test 5 mg.

of the dye per kilogram of body weight is injected intravenously; at the end of one-half hour a specimen of blood is obtained and examined. The retention of a measurable quantity of the dye, 10 per cent or more, is considered definitely abnormal and indicative of liver damage.

One of the carbohydrate tests of liver function, namely the galactose tolerance test, is sometimes of considerable value and particularly in markedly jaundiced patients in the differentiation between diffuse liver necrosis and duct obstruction. The test is of value especially in the early stages of the illness when the liver cell destruction on the one hand is at a maximum and when on the other hand the damaging effect of duct obstruction on the liver cells is still slight. When performed within two weeks of the beginning of the jaundice the test has considerable differential value. In the performance of the test, after a twelve-hour fast the patient is given 40 Gm. of galactose in 250 to 500 cc. of water; no food is permitted during the test but water can be taken as desired; the urine is collected for five hours and examined for sugar; the excretion of more than 3 Gm. of galactose is considered abnormal.

Other carbohydrate tests are occasionally used, namely, the levulose tolerance test and modifications of the glucose tolerance test, but they usually parallel more or less the findings with bromsulfalein and in general seem less helpful than the excretory tests.

Methods based upon the protein metabolism of the liver have not been strikingly helpful and are not widely used. If the changes in the blood plasma proteins may be considered in this light they may be of value in the absence of other causes of hypo-albuminemia.

The study of fat metabolism in this relationship is relatively new and not yet well evaluated. I am constrained to mention one such test because of its intriguing possibilities. Jones and Fish<sup>6</sup> have studied the curve of the plasma fatty acids after the injection of 0.5 cc. of adrenalin. They describe a normal curve and three different types of abnormal curves in association with diseases of the liver. They feel that the test offers prognostic aid in patients with liver disease and apparently regardless of the type of hepatic involvement. The curves A and B indicate a relatively excellent prognosis even

in the face of apparently severe liver injury provided adequate treatment is instituted, while the curves C and D suggest a prognosis of chronic invalidism or of a relatively short survival period. As far as I know these findings have not been extended or confirmed.

**Acute Diffuse Disorders of the Liver.**—The so-called "simple" or "catarrhal jaundice" may be taken as an example of an apparently primary acute liver disorder. It is now generally agreed that these cases represent a necrosis of liver cells rather than obstruction of the bile ducts. There are many grades of severity. A prodromal period of several days presents the symptoms of anorexia, gaseous eructations, feelings of fullness and of pressure in the epigastrium, nausea, and other gastro-intestinal symptoms. There may be slight fever for two or three days. The jaundice is obvious after a few days. If observed very early the van den Bergh test in the blood serum may give an indirect reaction but it soon changes to the direct reaction and bilirubin and bile salts are found in the urine. The stools may become progressively lighter in color and sometimes are completely acholic. As a rule the jaundice increases to a maximum and then gradually recedes. The liver is somewhat enlarged and often tender. The spleen is palpable.

In the presence of such a picture of a painless jaundice in a patient in the first half of life one is rarely in doubt concerning the diagnosis. Quite the opposite however is true of patients of middle age or more advanced age for these symptoms and signs may be duplicated by a gradual closure of the common bile duct by pressure from without, as from a carcinoma in the head of the pancreas. Here if used early the galactose tolerance test may be helpful. It may be necessary to observe the patient carefully for several weeks with close observation of the urine, of the stools and occasional quantitative tests of bilirubin in the blood serum. If the blood bilirubin reaches a maximum and then recedes and continues downward a favorable signal has been given. Jones and Eaton<sup>2</sup> suggest that a chart be kept of the daily fluid intake and urinary output so that one may recognize, when it occurs, the period of spontaneous diuresis that also signals the onset of recovery. In the most difficult cases, when the serum bilirubin has been indeterminate in its course for several weeks and the patient re-

mains deeply jaundiced, a surgical exploration is definitely indicated.

Although the prognosis in most cases of acute liver disorder is favorable, the course in certain instances is progressively from bad to worse, ending with the typical features of acute yellow atrophy with shrunken liver, deep jaundice, persistent vomiting, bleeding into the skin and mucous membranes, apathy, headache, confusion, delirium and unconsciousness.

The great diversity of etiologic agents in acute liver disorders may be appreciated by a study of the table from Bockus and Tumen,<sup>7</sup> entitled:

### HEPATOCELLULAR JAUNDICE\*

#### (A) CHEMICAL POISONS

1. Arsenobenzol derivatives—arsphenamine, neoarsphenamine, tryparsamide, etc.
2. Quinoline derivatives—cinchophen, atophan, quinophen, phenoquin, acophanyl, hydrocin, oxyliodide, arcanol, etc.
3. Halogen group—chloroform, carbon tetrachloride, tetrachlorethane, ethyl chloride, ethyl bromide, trichlorethylene, tribromethyl alcohol (avertin).
4. Aromatic organic compounds—trinitrotoluene (TNT), dinitrobenzene, dinitrophenol, picric acid, toluylenediamine, and acriflavine.
5. Miscellaneous—arseniuretted hydrogen, phosphorus, alcohol, lead, mercury, synthaline, snake venom.

#### (B) VEGETABLE POISONS

Mushroom poisoning.

#### (C) BACTERIAL OR VIRUS POISONS

Epidemic catarrhal jaundice (infectious jaundice), pneumonia, yellow fever, influenza, food poisoning, typhoid, paratyphoid, typhus and parenteric fevers, streptococcus septicemia.

#### (D) PROTOZOAL POISONS

Syphilis—icterus syphiliticus praecox, specific chronic interstitial hepatitis. Spirochaetosis icterohaemorrhagica, amebic dysentery, malaria, kala-azar, relapsing fever.

#### (E) MISCELLANEOUS

Idiopathic nonepidemic catarrhal jaundice (some types), toxemias of pregnancy, uremia, goiter, acidosis of recurrent vomiting in children, portal cirrhosis.

Certainly such a formidable list of potential poisons emphasizes the care with which the history must be taken.

\* Bockus, H. L., and Tumen, H. J.: *The Cyclopaedia of Medicine*, editor, G. M. Piersol, vol. vii, p. 588, F. A. Davis Co., Publishers.



In addition to these exciting causes of the disturbance the physician will be interested also in the known predisposing causes of acute liver disease, namely, a depletion in the glycogen reserve of the liver, anoxemia, the presence of a preexistent chronic diffuse disease of the liver, pregnancy and the puerperium, toxic thyroid states, or the presence of a syphilitic infection.

By the term **chronic diffuse hepatic disease** we mean **cirrhosis** since the latter term has come to mean a more or less diffuse increase in the fibrous tissue within an organ. The differentiation into portal cirrhosis and biliary cirrhosis is useful clinically and may have an important bearing from the therapeutic standpoint. The first type indicates an involvement particularly of the portal system, while the term biliary cirrhosis indicates a disease associated especially with chronic jaundice. In the later stages of each, both jaundice and portal obstruction may be present but the historical review of the case usually makes the distinction clear. The biliary type affects patients of the younger age group, while as a rule the portal type begins after forty. Both may have the history of an insidious onset but there is rather more likelihood of some evidence in the previous history of biliary or of hepatic disease in the biliary type than in the portal. The spleen is usually palpable in both types. The liver is uniformly enlarged in biliary cirrhosis and variable in size in portal cirrhosis. The size of the cirrhotic liver is determined not only by the disappearance of parenchymatous cells and the contraction of fibrous tissue that tend to decrease the size of the liver but also by the storage of fat and perhaps other materials that tend to make the organ larger.

In the well-developed portal cirrhosis the picture is unmistakable—the abdomen swollen with ascites, palpable spleen, dilated veins, and the pinched, emaciated subicteric facies. Advanced cirrhosis is the favorite proving ground for functional tests. Perhaps the most valuable here is the bromsulfalein excretion test and it should prove helpful if for any reason there may be a doubt as to the cause of the ascites. The blood plasma proteins are reduced and the hypo-albuminemia is especially striking. The laboratory examination of the ascitic fluid should be of value in differentiating between a transudate and an exu-

date. A complete study may be necessary for a full evaluation of the situation in cases where a chronic peritonitis or a tuberculous peritonitis has developed in the course of a cirrhosis, a not unusual combination.

Banti's disease, or primary splenomegaly, with the ultimate development of cirrhosis and portal obstruction is an important subdivision of the portal cirrhotoses for the surgical removal of the spleen may be an efficacious therapeutic procedure particularly if the operation is not too long delayed. The diagnosis may be made by the history of primary splenic enlargement or by the disproportionately large size of the spleen, together with the marked secondary anemia.

In biliary cirrhosis evidence of biliary obstruction or of infection of the biliary passages by examination of the duodenal contents suggests again definite surgical implications.

The occasional finding of a well-marked cirrhotic liver at necropsy in patients dead from some other cause and in whom the presence of cirrhosis was not suspected during life encourages us to believe that more careful clinical study and the judicious use of functional tests may enable us to make a diagnosis of liver cirrhosis earlier at a stage when therapeutic endeavors may be more successful than they are at present. The patient of middle age with a definite history of chronic and excessive alcoholism and of gastro-intestinal disturbances should certainly be fully investigated from the standpoint of a possible cirrhosis of the liver. Minimal requirements for such a study should include a careful physical examination, a roentgenographic study of the esophagus, the van den Bergh reaction of the blood serum, the estimation of the blood plasma proteins, and the bromsulfalein excretion test.

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### THE SIGNIFICANCE OF ACUTE HYPOTENSION; ITS ETIOLOGY AND TREATMENT

IN a variety of conditions the systolic arterial blood pressure, as customarily measured, may be observed to be below the accepted normal standards, which vary with age from 100 to 140 mm. of mercury. But the term "hypotension" had best be reserved to designate a systolic pressure persistently less than 100 or—and more important—a pressure abruptly reduced from a value within normal limits or even above. The chief symptoms of this condition such as dizziness, "faintness," weakness and fatigue, appear to depend more upon insufficient blood flow than upon the precise level of arterial pressure. Certain others—hyperpnea and tachycardia—are suggestively analogous to the effects produced experimentally in animals by the sudden reduction of blood pressure within the carotid sinus.

The subject has been fully reviewed in the excellent monograph by Friedlander.<sup>3</sup> In this paper the mechanisms concerned with acute hypotension will be briefly discussed and illustrated.

*The control of arterial blood pressure* is normally effected by the coordinate interplay of three major factors: (1) the cardiac output, (2) the volume of the circulating blood, and (3) the state of the blood vessels, including the peripheral vascular resistance. These are interdependent, as a consequence of certain reflex mechanisms mediated through sympathetic and parasympathetic pathways, to such a degree that variations in one factor lead to compensatory changes in the others. Certain qualifications of these factors merit emphasis.

**Cardiac Output.**—Provided the venous inflow remains constant the output per minute of the normal heart remains unchanged despite considerable alterations of arterial resistance or of cardiac rate. On the other hand, increase or decrease in the volume of blood entering the heart from the great veins results in conspicuous increase or decrease in cardiac output. It is thus apparent that the output of the heart is dependent principally upon the condition of the venous circulation, and that the contribution of cardiac output to arterial pressure depends upon the relation between the amount of blood leaving the arteries via the capillaries and that entering the ventricles from the auricles and veins. The optimum conditions are fulfilled when venous inflow is sufficient to fill the ventricles during diastole to their maximum capacity for discharge. If ventricular filling is impeded, as in some cases of mitral stenosis or with constrictive pericarditis or pericardial effusion, the systolic pressure diminishes unless balance is restored by arteriolar constriction. Obviously, too, though venous inflow be unaltered, cardiac output will fail if the functional capacity of the heart muscle is reduced (myocardial disease, coronary occlusion) or if the rate of the heart beat is so excessively rapid as to prevent adequate filling during diastole (paroxysmal tachycardia, auricular flutter, or auricular fibrillation with rapid, irregular ventricular beat).

**Volume of the Circulating Blood.**—Reduction of total blood volume (*e. g.*, following hemorrhage or severe diarrhea) may occur without demonstrable fall of arterial blood pressure in so far as this may be met by reduction of the capacity of the vascular system by constriction of the vessels. Beyond this point pressure in the arteries may fall due to insufficient filling. But, with or without alteration of the *total* volume of circulating blood, changes in the *distribution* of the blood may strikingly influence the arterial blood pressure. The most effective element of blood volume as regards arterial pressure is that portion thereof contained at any moment in that section of the cardiovascular system between the heart and the arteriolar ends of the capillaries. Any shift of blood volume to the disadvantage of this portion will lead to a reduction of arterial pressure unless compensation can be effected by con-

striction of arteries, arterioles and the arteriolar-capillary limits.

**State of the Blood Vessels Including Peripheral Vascular Resistance.**—There is little proof that changes in elasticity of the larger arteries such as develop with advancing age contribute to hypotension, although the effect of hypotension in provoking symptoms of inadequate blood flow to the brain is undoubtedly enhanced if such flow is already impaired by sclerotic changes in the cerebral arteries. There is evidence that loss of intrinsic venous tone with consequent "pooling" of blood in splanchnic or dependent areas, may, under certain conditions, contribute to the development of circulatory collapse, and that the massaging support rendered to the veins by the movements and tone of the muscles of the extremities is of considerable importance in forwarding the return of blood from the periphery. But in the vascular field between arteries and veins lie the chief resources for the sensitive control of arterial pressure. Upon the integrity of these mechanisms depends the adaptation of blood flow to meet local circulatory requirements, and to counterbalance the hydrostatic effects of changes in posture.

The peripheral vascular resistance is determined by the total cross-sectional area of the smaller vessels—arterioles, capillaries and probably the venules. The caliber of these is regulated in part directly and in part by vasomotor nerves. They react diffusely or locally to changes in the temperature of their contents or environment—dilating with heat and constricting with cold—and to chemical alterations in the blood or tissue fluids—dilating under the influence of certain blood-borne drugs or substances produced elsewhere in the body (histamine) and constricting under the action of others (adrenalin). The products of tissue metabolism or injury have a decided dilating effect upon this portion of the vascular field. Finally, by far the most sensitive control of vascular caliber is reflexly mediated by the vasomotor nerves—chiefly vasoconstrictor—from centers in the medulla and spinal cord.

The accepted standards for blood pressure have already undergone some revision since this observation became a routine with the introduction of manometric methods. Thus, clinical experience, as well as that of insurance companies, has

emphasized the significance of the diastolic values as well as the systolic, particularly in cases of hypertension. Here too, the importance of repeated estimations of blood pressure has become apparent in view of its fluctuation in some individuals at rest between normal and high values. Persistent hypotension has not escaped detection in the routine measurements of blood pressure, but, except as a result of special studies,<sup>6</sup> too little information is available concerning the transient changes in blood pressure which result from alterations of posture.

When a human being rises from the horizontal to the vertical position and stands quietly, the physiologic demands upon the circulation are considerably altered. Probably least significant is a slight but definite increase in the total oxygen consumption (5 to 20 per cent). More important is the hydrostatic effect of gravity upon the blood in the vessels. This tends to enhance the flow of blood downward out of the arteries into the veins below the heart but to hinder the flow upward in the dependent portions of the venous system.\* All of the above-mentioned factors fundamental to the control of the arterial blood pressure are thus adversely affected: a larger proportion of the total blood volume tends to accumulate on the venous side of the circulation and, despite this, the return of venous blood to the heart, so essential to adequate diastolic filling of the ventricle, is decreased, and systolic discharge is thus diminished. Moreover, the circulation to the medullary and cerebral centers suffers the potential disadvantage of a change from approximately heart level to a position 25 cm. or more above.

In the normal individual compensatory circulatory adjustments are quickly made to meet these conditions and are more or less adequately maintained. The systolic blood pressure alters only slightly. The diastolic pressure rises, reducing the pulse pressure and indicating constriction of the peripheral arterioles in accommodation to the tendency toward increased outflow. The cardiac rate increases, maintaining the total cardiac output by increasing the number of ventricular systoles and thus accommodating to the decreased diastolic filling con-

\* Of the total capacity of all the blood vessels two thirds or more lie below the level of the heart in the erect posture.



sequent upon the decreased inflow of venous blood. The integrative control of these mechanisms is still not clearly understood, but the importance of the various vascular and nervous phenomena is emphasized by the results observed when one or another phase thereof is temporarily or permanently impaired.

**Imperfect Circulatory Adjustment to Changes in Posture.**—Probably everyone has experienced a transient sensation of weakness and dizziness upon standing erect after sitting or lying in a hot bath. The vascular dilatation produced by heat is often widespread, and at the same time the reactivity of the vessels to vasoconstrictor impulses is temporarily reduced. The result of a transient impairment of this element of the circulatory adjustment to change in posture is thus exemplified.

More frequently imperfect postural adaptation becomes apparent only when one or another of the various phases thereof tends to become insufficient as the circulatory strain continues. The observations of Turner, Newton and Haynes<sup>40</sup> have demonstrated that such circulatory adjustments are maintained with varying degrees of success by healthy subjects during a fifteen-minute period of quiet standing; some individuals become dizzy or actually faint after a period of eight minutes. In such circumstances stagnation of blood in the legs is demonstrable as an increase in leg volume, and pooling in the splanchnic area is suggested by the improvement in circulatory adjustment to posture which can be effected with an abdominal support (corset or bandage). Similar episodes characterized by faintness, weakness and excessive tachycardia on quiet standing are not infrequent after infectious diseases, particularly influenza, or after an individual has been confined to bed for long periods. Here both the relatively unstable vasomotor response, and the loss of support to the venous circulation afforded by the normal tone of the leg muscles impair the circulatory adjustments.

Recently several reports in the German literature have directed attention to a form of transient hypotension known as "gravity shock."<sup>41</sup> If, after strenuous exercise (sprinting), an individual stands quietly erect instead of lying down, there first ensues a fall in blood pressure and pulse rate from elevated to normal levels. This observation is analogous to that

which is customarily applied in examining a patient suspected of circulatory disease, except that it is the usual practice to put the patient through a milder form of exercise and then to place him at rest. The speed with which pulse rate and blood pressure return to normal is taken as a measure of fitness. In Mateeff's subjects there was no question of cardiovascular diseases; all were young people in athletic training. He observed that, after the pulse rate had returned to normal, if the subject remained standing, the circulatory adjustments to the erect posture tended to disintegrate: the pulse rate rose anew, the diastolic pressure rose to approach the systolic and finally both systolic and diastolic pressures fell together with the onset of circulatory collapse. Compensation was immediately restored when the horizontal posture was assumed. This, together with the fact that the development of such a condition could be prevented by bandaging the lower extremities immediately after exercise, led Mateeff to the conclusion that the fundamental cause lay in the extreme hyperemia in the leg muscles after the work. To the pooling of blood in these areas, with consequent decrease in rate of return of venous blood and secondarily deficient cardiac output, was ascribed the series of events observed.

As demonstrated by Weiss and his collaborators,<sup>7, 7a</sup> small doses of sodium nitrite, insufficient to provoke any considerable circulatory alterations with the subject supine, may yet so impair the circulatory adjustments necessary in the upright position as to lead to collapse. The effect of such amounts of nitrite is not to produce dilatation of the arterioles. These vessels maintain their tone and reactivity; they even constrict in the attempt at adjustment. Weiss *et al.* have adduced evidence to show that the primary effect of sodium nitrite is exerted upon the venous side of the circulation, impairing venous tone and resulting again in a disproportionate distribution of blood to the disadvantage of the arterial system.

All these examples of faulty circulatory adaptation to the erect posture have a common basis in the eventual stagnation of blood in the dependent portions of the capillary and venous vascular beds. As a consequence the return of venous blood to the heart is progressively reduced, its systolic discharge is lessened and, despite the increase in heart rate, the arterial

system is less and less adequately distended. Constriction of the peripheral arteries is not only unimpaired but increases, thereby maintaining and even elevating the diastolic pressure, up to the moment when collapse supervenes due to insufficient blood supply to the medullary and cerebral centers.

*Treatment.*—In such circumstances little benefit is to be anticipated from the administration of substances which enhance or maintain constriction of the peripheral elements of the arterial system. Of primary importance are measures calculated to prevent the pooling of blood in the extra-arterial portions of the vascular system and to foster the return of venous blood to the heart. The most beneficial is that which is the natural consequence of collapse: the reassumption of the horizontal position. Symptoms are dramatically relieved and the blood pressure and flow return to normal almost at once if the patient is caused to lie down. In most instances the onset of symptoms can be delayed or averted if the patient wears an inelastic abdominal support—corset, girdle or broad belt. In so far as the strength and tone of the muscles of the extremities may be improved by massage and exercise the supporting effect thereof upon the peripheral venous channels may be enhanced. Such measures are of particular value during convalescence from severe infection or prolonged illness of any sort. Sometimes the additional support of elastic stockings, temporarily applied, may be beneficial.

**Orthostatic Hypotension.**—In sharp contrast to these examples, in which circulatory adjustments to the upright position are performed but gradually become inadequate, stands the condition known as "orthostatic or postural hypotension." The distinction lies in the immediate and more or less complete failure of such adaptation as soon as the upright posture is assumed. First described by Bradbury and Eggleston,<sup>1</sup> about 30 cases of this syndrome have been reported, having the following characteristics in common: (1) immediate, pronounced and persistent fall of the systolic blood pressure, frequently as great as 50 mm. of mercury, when the patient stands; (2) a synchronous but usually smaller drop in the diastolic pressure; (3) absence or diminution of the increase in heart rate normally demonstrable upon rising to the upright position, and (4) dizziness, faintness and collapse. Additional

symptoms and signs less uniformly to be observed are: (1) orthostatic oliguria, (2) absence or suppression of sweating over part or all of the body and, perhaps, as a consequence, (3) increased distress in hot weather or hot rooms.

The observations of Ellis and Haynes,<sup>6b</sup> which include detailed examination of the circulatory dynamics in this condition, indicate that the fundamental abnormality is the failure of the reflexes which normally bring about vasoconstriction and more rapid heart rate when the patient stands. The cardiac output is not markedly changed but the blood circulates mainly through the dependent portions of the circulation. The brain receives an inadequate share of blood, and dizziness and faintness result. These circulatory phenomena, together with the hypohidrosis frequently observed, suggest some functional or anatomical impairment of the sympathetic nervous system as etiologic factors. Indeed, many of the reported instances of orthostatic hypotension have been associated with disease of the central nervous system. Similar failure of orthostatic control of blood pressure has been reported following section of anterior motor roots in the lower thoracic and lumbar regions in patients with hypertension.<sup>2</sup>

*Treatment.*—Here, too, mechanical measures such as an abdominal support or elastic stockings calculated to reduce the capacity of dependent portions of the vascular system may sometimes assist in averting the development of symptoms. But, and again in contrast with the cases of imperfect postural adjustment, in "orthostatic hypotension" drugs which promote and maintain vasoconstriction often offer considerable relief. The most valuable substance is ephedrine, the action of which is relatively prolonged. It may be given in doses of 25 to 50 mg. by mouth, commencing before the patient arises in the morning and continuing at intervals of two to four hours until the late afternoon. Too large or too frequent doses may cause unpleasant symptoms and insomnia. Recently the use of benzedrine has been reported as efficacious in orthostatic hypotension.<sup>4</sup> The fact that, in the case of both ephedrine and benzedrine, symptomatic relief may be obtained without entirely preventing the orthostatic fall in pressure suggests that the beneficial effect may be upon the brain as well as upon the peripheral vessels.

## TABULATION

	Imperfect circulatory adjustment to upright posture.	"Orthostatic hypotension."
Systolic pressure.	Maintained up to the point of collapse—then falls abruptly.	Falls immediately on standing.
Diastolic pressure.	Rises gradually to point of collapse—then falls abruptly.	Falls immediately on standing.
Heart rate.	Increases.	Remains unaltered or increases abnormally little.
Cardiac output.	Gradually decreases.	Maintained.
State of peripheral vessels.	(1) Arterioles constrict. (2) Veins, venules and probably capillaries dilate.	Arterioles fail to constrict.
Mechanism.	Pooling of blood in dependent <i>venous</i> portion of vascular bed at expense of <i>general arterial</i> blood volume.	Increase in proportion of blood in <i>all</i> dependent vessels— <i>arteries and veins</i> —at expense of that in vessels above level of the heart.

**Shock.**—Hypotension caused, at basis, by absolute reduction in volume of the circulating blood is exemplified by "shock" or "surgical shock." This is a condition of acute circulatory failure characterized by both low arterial and low venous pressures. The critical reduction of blood volume may be evoked by: (a) loss of blood by hemorrhage, (b) extravasation of blood or serum due to bruising, cutting, burning or freezing, (c) transudation of the fluid constituents of the blood through the capillaries as a result of chemical injuries which apparently effect a widespread increase in capillary permeability, or (d) by excessive fluid loss in proportion to fluid intake (dehydration) as in cases with profuse diarrhea or diabetic acidosis.

In the early stages of collapse such as follows immediately upon injury ("primary shock") there is vasodilatation but in the later phase, when circulatory failure becomes established,

the peripheral resistance is demonstrably increased and the volume flow of blood is greatly reduced. This state of the circulation, present with the patient in the horizontal position, may be likened to that described under imperfect postural adaptation above. The arteries fail to contain a proportion of the blood volume sufficient to maintain the normal blood pressure; return of venous blood is impaired by pooling or stagnation, usually in visceral venous areas, and the low venous pressure is insufficient to foster adequate systolic discharge. If the blood pressure remains low for more than a short period, fluid and electrolytes escape from vessels to the tissues and the blood volume may be still further reduced.

*Treatment.*—Except in the early (“primary”) stages adrenalin or ephedrine is without benefit. Treatment must be directed to restoring the blood volume. This may be accomplished by transfusion, and should be undertaken as soon as, or if possible before, signs of falling pressure appear.

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## CLINIC OF DR. FRANK R. FORD

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#### THROMBOSIS OF THE CEREBRAL ARTERIES WITH A DISCUSSION OF HEMIPLEGIA<sup>1</sup>

**Members of the Third Year Class.**—The subject of to-day's discussion is that of thrombosis of the cerebral arteries. As you know, the nervous system is nourished, just as are the other organs, by its blood supply and interruption of the blood supply results in necrosis of the tissue with softening, or as we say, infarction. The commonest neurologic syndrome resulting from thrombosis of the cerebral arteries is hemiplegia. This condition is important not only because it is so common but because many of the fundamental principles of clinical neurology are based upon the study of the phenomena observed in the course of a case of hemiplegia. These principles you will find necessary for the analysis of other neurologic syndromes which you will encounter in the future. I shall, therefore, discuss the matter in considerable detail. This patient will serve to illustrate most of the facts I wish to bring out. I may say at once that we believe that this patient has had a large lesion of vascular origin centering about the fissure of Rolando in the right hemisphere, which has destroyed the anterior and the posterior central gyri and has caused left hemiplegia and left (cortical) hemianesthesia.

This patient, a colored man of thirty-six years, was not conscious of any departure from his usual good health until some fifteen months ago. At that time he was lifting a heavy weight and suddenly felt dizzy and nauseated. Within a few minutes he became unconscious and had several convulsions involving the left arm and leg. He was brought to the hospital where he remained in a state of unconsciousness or confusion for several days. During

<sup>1</sup> This is the first of 8 clinical demonstrations which are given to the students of the third year class in neurology during the first quarter of the year.

this period his head and eyes were turned to the right side and his left arm and leg were flaccid and immobile. The left cheek moved in and out during respiration showing that even the facial muscles shared in the loss of tone. The tendon reflexes were absent on the left for several days. His bladder was distended and had to be emptied by catheter. The left hand was warm and dry during this period and within a short time began to show slight edema. His blood pressure was elevated to 210/115 and there were evidences of sclerosis of the peripheral and the retinal arteries. The Wassermann test was negative in the blood and spinal fluid.

On the fifth day the patient began to regain consciousness and was able to cooperate for a few minutes during the examination. It was found that the patient could not move the left arm or leg. The left side of the mouth showed very little movement but he was able to close the eyelid and wrinkle the forehead almost as well on one side as the other. The chest moved freely on both sides but it was found that the movements were somewhat smaller on the left side than on the right. This was true of spontaneous breathing as well as voluntary breathing. The head could be lifted from the pillow and rotated fairly well to either side. The eyes still showed a tendency to deviate to the right and the patient could not move them to the left beyond the midline. Articulation was indistinct. There was some difficulty in emptying the bladder. The tendon reflexes were present on both sides and about equally active. The abdominal reflexes were absent on the left. Sensibility seemed to be much diminished over the entire left side of the body, but it was impossible to make a satisfactory examination owing to the patient's diminished power of attention.

The patient's condition slowly improved and about four weeks after the onset of the illness he began to regain power in the left leg. He was permitted to return home. Convulsive seizures involving only the left side continued to occur at intervals of two or three months. His blood pressure remained about 200/115.

A complete neurologic examination was made in the out-patient department seven months after the illness, which revealed the same condition which the patient presents today. You can see that the patient's eyes are moved freely in all directions and that his face is almost symmetrical. There is, however, a slight increase of muscle tone on the left side of the face which is shown by moderate deepening of the nasolabial fold. Now, when the patient shows his teeth, you can see that the left side of the mouth moves almost as well as the right side, although close observation will reveal a slight delay in the movement and a slight reduction of the excursion. When the patient laughs, however, the movement of the left side of the mouth is actually greater than that of the right side. The functions of the other cranial nerves are preserved. His tongue is protruded in the midline and can be moved easily to either side, although in some patients suffering from this same condition the tongue may deviate a bit to the side of the paralysis. You have noticed, no doubt, that the patient's left arm is held in a peculiar position. It is adducted and internally rotated at the shoulder, flexed to almost 90 degrees at the elbow, pronated in the forearm, and flexed at the wrist and finger joints. The leg, on the contrary, is adducted and extended at all joints. You will notice that



when I try to extend the arm I meet with considerable resistance, but flexion is much easier. The arm is held in this position as a result of increase of muscle tone in certain groups of muscles. This statement also applies to the leg which can be passively flexed only by the exertion of a great deal of strength but may be extended quite easily. As I flex the leg there is strong resistance to the movement at first, but as the movement is continued the resistance melts away so that the leg can be flexed with little effort. You see now that the leg is maintaining the position of flexion which I imposed upon it, although I have withdrawn my hand. As I try to extend it now I meet with some little resistance. The muscles, therefore, have a property which might be termed *plasticity*. Stimulation of the sole of the foot will relax the extensor tone at once and the leg is then easily flexed. This peculiar type of rigidity is properly termed *spasticity*, a condition which has been precisely defined by Walshe. The patient has never recovered the proper use of his left arm and leg and I will now show you the extent of his disability. You will note that he can walk, but the left leg is not moved normally. The leg is not fully flexed at the knee as it is brought forward and the toes are not lifted from the floor. The leg is advanced chiefly by rotating the pelvis, using the right leg as a pivot. To clear the left toes, which would scrape the floor, he swings the foot in a semicircle. The leg is used somewhat as an artificial leg might be used, that is, as a prop. The patient can grasp my hand with some force, but you will notice when he makes a maximum effort, the elbow is somewhat flexed, the forearm pronated and the arm abducted at the shoulder. He cannot squeeze my hand without making these movements at the same time. He cannot flex one finger without flexing all the other fingers as well as the thumb. When he tries to flex the elbow, the arm is also abducted a bit and the fingers close. In the same way he cannot abduct the arm at the shoulder without flexion of the elbow and fingers. When I ask the patient to extend the fingers, there is very little movement of the fingers, but there is some extension at the elbow and adduction at the shoulder. When he makes one of these movements the others invariably occur. I shall now place him on the couch in order to examine the leg. When he tries to flex the hip, which he does with great difficulty, there is also flexion of the knees and dorsiflexion of the foot. The attempt to flex the knee causes flexion of the hip and dorsiflexion of the foot. He cannot move the foot or the toes without flexing the hip and knee at the same time. The patient has therefore lost the ability to perform isolated movements involving single muscle groups, and such movements as he can perform are always mass movements. Foerster terms such mass movements *synergies*. The chest still moves less on the left side than on the right. It is impossible for you to see this difference from the benches, and it is really very slight. We have made many graphic records of his chest movements, however, and you may take my word for it. The patient can now empty his bladder with very little difficulty, but he complains of frequency. It has been shown in similar cases of hemiplegia that the bladder is small and that the stretch reflex is increased. The tendon reflexes are all much exaggerated in the left arm and leg. The activity of the tendon reflexes corresponds to the distribution of tone in the muscles. Thus, the biceps reflex is more active than the triceps, the knee jerk is greater than the hamstring reflex. The

plantar reaction is a typical Babinski reflex. You see that the great toe is slowly extended (dorsiflexed) in a well-sustained movement and at the same time the small toes are spread apart and also somewhat extended. There is a well-sustained ankle clonus. The abdominal reflex has now returned but is easily exhausted by a few strokes.

The patient is conscious that sensibility is deficient over the left side of the body, especially in the left hand and foot. You will note, however, that he can distinguish the sharp end of the pin from the dull end. In the same way he can distinguish heat and cold. These modalities of sensibility are not normal but they are not lost. Now I take the patient's left forefinger and move it up and down. The patient cannot recognize these movements even when they are relatively gross. He cannot find the left hand with the right when his eyes are closed. In the same way he cannot localize a touch on the left arm or leg and cannot guess whether I am applying both points of a compass or just one point.

The left hand is now cold and rather moist. You will recall that during the early part of his illness the left hand was warm and dry. The edema which was present at first has now disappeared.

These facts will be somewhat clearer if I offer an interpretation. You will recall that the patient's illness began with a convulsion confined to the left side of the body. Movements of the left side of the body are represented in the motor cortex of the right hemisphere. Sudden interruption of the circulation caused anoxemia which for a time caused excitation. As a result, the functions residing in the affected area were discharged in an explosive fashion and a convulsion took place. We classify convulsive seizures of all types among the symptoms due to *discharge of function*. Such phenomena are not peculiar to the motor cortex. Discharges involving numerous other cortical areas are well known. When the postcentral convolution is affected, the patient experiences paresthesias over the opposite side of the body. Olfactory and gustatory hallucinations occur in discharges involving the uncinate gyrus. Visual hallucinations of a crude nature are associated with discharges in the occipital cortex and more elaborate visual phenomena with discharges of cortical areas in the temporal lobes. Even the lower centers of the brain stem and spinal cord are capable of discharge.

After the convulsion the patient remained unconscious for several days. His left arm and leg were quite flaccid and devoid of tone; the tendon reflexes were abolished on that side. As you know, the tendon reflexes are dependent upon the spinal

reflex arcs. Consciousness does not reside in any sharply localized part of the brain. Evidently the sudden insult to the brain resulted in transient but widespread disturbances which affected not only the brain but the spinal segments as well. We may attribute such symptoms to neurologic *shock* for lack of a better term. Such symptoms do not occur in cases of slowly progressive hemiplegia due to tumors of the brain.

After consciousness was regained it was found that there was loss of isolated voluntary movements of the left arm and leg and also disturbances of sensibility over the left side of the body, involving chiefly sense of passive movement, sense of position, tactile localization and two-point sense. It is well established that isolated volitional movements are dependent upon the integrity of the motor cortex and that the type of anesthesia with which we are dealing indicates injury to the postcentral convolution or to its projection pathways. The patient, therefore, suffers from *loss of function* of both the motor and the sensory cortex.

Several weeks after the onset of the illness, the patient's condition began to change. The affected extremities grew spastic and began to assume a peculiar posture with the arm in flexion and the leg in extension. The tendon reflexes became grossly exaggerated. Plantar stimulation caused dorsiflexion of the great toe. Such signs cannot be due to loss of function for they are obviously due to excessive and uncontrolled activity of some part of the nervous system. It is customary to term them symptoms due to *release of function*. In the analysis of release phenomena we must always ask ourselves two questions: (1) what structures are released? and (2) what structures are destroyed? There is abundant evidence derived from clinical observation and from experimental investigation to show that these particular signs are due to release from cortical control of the spinal reflex arcs and of certain structures lying within the hindbrain which many observers identify with the vestibular nuclei. These structures seem to be important elements in the complex nervous mechanism which maintains muscle tone and posture and their release results in the development of the peculiar posture observed in hemiplegia. Walshe has shown that this hemiplegic

posture is an exaggeration of our normal standing posture. From the physiologic point of view, hemiplegia has a close relationship to decerebrate rigidity in the experimental animal. The gross exaggeration of the tendon reflexes is regarded as evidence of loss of inhibition of the spinal reflex arcs. Ankle clonus is merely a series of tendon reflexes. Study of electromyographic records indicates that each beat of the clonus is associated with a single diphasic action current in the muscle such as occurs in a tendon reflex. Sudden pressure on the sole of the foot stretches the extensors of the ankle which contract just as they do when the tendo achillis is struck with the percussion hammer. The foot is therefore abruptly extended and the dorsiflexors are stretched, resulting in a reflex contraction of the flexors. One reflex thus provokes the next reflex. The plantar reflex also requires some comment. Babinski was the first to show that in disease of the pyramidal tract, stimulation of the outer aspect of the sole of the foot causes dorsiflexion of the great toe and abduction of the small toes. Walshe has shown that this movement is merely a part of a more extensive movement of triple flexion by which the foot is withdrawn from potentially injurious stimuli. It may, therefore, be regarded as a spinal reflex of defense. The reflex is best elicited from the sole of the foot but may be produced by strong stimuli applied to any part of the lower limb or even to the abdomen in certain cases. Although the Babinski response often offers some difficulty in interpretation, the existence of a typical reaction constitutes the most reliable clinical evidence of disease of the pyramidal tract. I must now discuss the second question. What structures must be destroyed to produce spasticity? Do the corticospinal fibers which activate the spinal motor neurons in volitional activity also convey inhibitory impulses to these neurons? This problem is still a subject of debate, and I cannot give you a definite answer. The neurons which give rise to the fibers of the pyramidal tract are found in the cortex just anterior to the fissure of Rolando. This region has been termed area 4 by Brodmann. Just anterior to area 4 is another histologically defined area termed by Brodmann area 6. John Fulton and his collaborators claim, chiefly on the basis of experimental work, that lesions in area 6 cause spasticity with little or no

paralysis and that lesions in area 4 cause paralysis without increase of muscular tone. Typical hemiplegia with spasticity results when both of these areas or their projection pathways are destroyed. This view is strongly opposed by Walshe for a variety of reasons. He cites several cases in man, in which careful excision of area 4 has been performed with resulting hemiplegia and spasticity. Foerster, who has had an unrivaled experience in cortical excision in man, also states that ablation of area 4 alone causes typical hemiplegia with spasticity, and that ablation of area 6 a  $\beta$ , which constitutes the larger part of area 6, is associated with no demonstrable signs or symptoms whatever.

The improvement in the patient's condition during convalescence requires some consideration. It is a firmly established teaching that neurons of the central nervous system cannot regenerate. Destruction of a neural pathway must, therefore, result in irreparable damage. Nevertheless, the patient improved to some extent. He regained the power to move the extremities, to empty his bladder, and to walk. It is customary to divide the period of improvement into two stages. During the first stage, which lasts only a few days or weeks, improvement is rather rapid and may be due chiefly to the disappearance of shock. The second stage lasts for a year or more and improvement during this period is more gradual. Hughlings Jackson has discussed this tendency to improvement following injuries to the nervous system under the term of *compensation*. According to Jackson, those structures which contribute to the return of motility can produce only those movements which they produced under normal conditions before the lesion developed. Jackson believed that the movements of each side of the body are represented in both hemispheres although to different degrees. Isolated movements of the extremities are represented almost entirely in the contralateral motor cortex and to a minimal degree in the homolateral cortex. Consequently when the contralateral motor cortex is destroyed, as it is in the present case, such movements can be regained to only a limited extent and then after long training. Other movements are affected to varying degrees. Many years ago Broadbent pointed out that movements are preserved in hemiplegia in proportion to their bilaterality. Strictly

unilateral movements, such as isolated movements of the extremities, are completely lost and are never regained; movements which are sometimes bilateral and sometimes unilateral, such as those of the shoulders and hips, are regained to a large extent; and movements which are always bilateral, such as those of the eyes, larynx, pharynx, chest, abdomen and spine, are never more than slightly affected. Movements of the last type are of course represented almost equally in the two hemispheres. The study of cases of bilateral hemiplegia lends strong support to the theory that certain movements have bilateral representation in the cortex. Bilateral lesions in the motor cortex cause not only paralysis of the extremities, as in hemiplegia, but also pseudobulbar palsy, in which paralysis of the larynx, pharynx, jaws and face may occur. Moreover, there is a striking weakness of all the muscles of the trunk.

The mass movements of the affected extremities, termed synergies by Foerster, arise, he claims, in certain areas in the contralateral cortex which have escaped injury. These are area 6 of Brodmann which lies in the superior frontal convolution, area 5 in the superior parietal convolution, and area 22 in the superior temporal convolution. These are not connected with the spinal cord by way of the pyramidal tracts but influence the spinal cord indirectly by way of lower centers. Foerster states that electrical stimulation of these areas when they are exposed at operation causes the same mass movements which the hemiplegic patient produces voluntarily. Moreover, spontaneous discharges arising in such areas cause convulsions in which mass movements occur. When these areas are excised in hemiplegic patients, there is a great reduction in the remaining motility.

You will remember that during the first few days of this patient's illness there was retention of urine and since then there has been mild frequency of urination. Langworthy has shown that in such cases the bladder is small and that the stretch reflex is increased. It will not be amiss, therefore, to say a few words about the innervation of the bladder. As you know, the bladder receives a segmental nerve supply from the lumbar and sacral segments of the cord. It has been shown that there is also a mechanism located in the midbrain which exerts an important effect on the tone of the bladder

musculature. Voluntary control of the bladder, however, is vested in the upper part of the motor cortex on the mesial surface of the hemisphere. This representation is of course bilateral, and unilateral lesions never cause more than mild or transient disorders of bladder function. The initial retention in hemiplegia is probably due to shock involving the segmental mechanisms, whereas the frequency which appears later is probably to be attributed to release of the spinal and midbrain mechanisms. The behavior of the smooth muscle of the bladder, therefore, is in many ways similar to that of the striated muscle of the extremities.

The vasomotor disturbances present in the affected hand deserve some comment. Such conditions are not always demonstrable and when present are not always the same. However, the conditions observed in this patient are, in my experience, both common and characteristic. In most cases the hand is warm, dry, pink and slightly edematous during the first few days after the onset, and subsequently it becomes cold, wet and slightly cyanotic. In a small percentage of cases there is massive edema and outspoken elevation of temperature in the affected extremities during the first stage of the illness. The temperature may be elevated more than  $1^{\circ}$  C. The interpretation of such changes is still uncertain. One might assume that in the initial stage we are dealing with the effects of shock upon the segmental autonomic reflexes which control sweating and vasomotor reactions and that subsequently the reverse effects are caused by release of the same reflexes. This cannot be regarded as more than an attractive hypothesis at present.

The sensory disturbances must now be taken up. As a result of the investigations of Henry Head and of Gordon Holmes, it is known that the cerebral cortex is not necessary for the appreciation of crude sensations of touch, pain, heat and cold. The thalamus is capable of subserving such modalities of sensibility. The cortex, however, is necessary for the recognition of passive movements, of position, of localization of stimuli and for the appreciation of differences and degrees of tactile and thermal stimuli. A little reflection will convince you that the function of the sensory cortex is that of interpretation, synthesis and analysis of simple sensations.

This patient shows loss of these functions and he may, therefore, be said to have *cortical anesthesia*. It is important to keep in mind that special tests are required for the demonstration of anesthesia of this type, for hemianesthesia is just as significant of cerebral damage as is hemiplegia and may be overlooked if proper tests are not applied. The disturbances of tactile and of thermal sensibility are of such a nature that quantitative tests must be applied to demonstrate them. Such tests are therefore not suitable for practical clinical neurology. The tests for appreciation of position and passive movement and the compass test for two-point sensibility are so simple that they should be employed as a routine in every examination of a patient suffering from disease of the nervous system.

Thrombosis of the cerebral arteries may result from a large number of conditions. In general, it may be said that it may be the result of any change in the properties of the blood which favors clotting or of any disease of the arteries. The possible causes are, therefore, almost innumerable. In the vast majority of cases, however, the patient is suffering from cerebral arteriosclerosis with or without hypertension. It must be borne in mind that the degree of sclerosis of the cerebral arteries is not always equal to that of the peripheral or retinal arteries. We have seen advanced changes in the cerebral arteries in patients whose peripheral arteries were soft. Moreover, arteriosclerosis is not confined to elderly subjects, for young adults and, in rare cases, even children may develop the same changes. The second commonest cause of thrombosis of the cerebral arteries is syphilis. We should always investigate the possibility of syphilis whenever we find evidences of cerebral vascular disease. Certain acute infectious diseases, such as typhoid fever, scarlet fever, diphtheria and numerous others, may cause lesions in the arteries which occasionally lead to thrombosis. In some cases proliferation of the intima of a cerebral artery leads finally to occlusion of the lumen, giving rise to symptoms identical with those of thrombosis. Embolism is another possible cause of cerebral vascular occlusion. As a rule cerebral emboli arise as a result of endocarditis or of detachment of bits of mural thrombi from seriously diseased hearts. Rupture of cerebral arteries with hemorrhage into the brain is not uncommon, but is probably less frequent than



thrombosis. It is a result of hypertension in most cases. As a rule hemorrhage is associated with a greater degree of shock at the onset and, moreover, leads to the development of increased intracranial pressure in many cases. The spinal fluid may contain blood. The mortality is much higher in cases of intracranial hemorrhage than in cases of cerebral softening due to thrombosis.

The study of cases of thrombosis of the cerebral arteries has led to the accumulation of a great deal of information about the distribution of the arteries and about the functions of various parts of the brain; for the occlusion of any given artery produces a lesion of almost constant extent and an almost constant group of symptoms. Foix and his collaborators have taken a leading part in this work. It is impossible to review this whole field in the short time at my disposal, but I shall mention the more important syndromes in brief, deferring a more complete discussion to another time.

The chief arteries which supply the brain are the anterior, middle and posterior cerebral arteries. The two anterior cerebral arteries are united by the anterior communicating artery, and the middle cerebral arteries are joined to the posterior cerebral arteries by the posterior communicating arteries. The posterior cerebral arteries are formed by the bifurcation of the basilar artery, which is formed by the union of the vertebral arteries. Thus an unbroken arterial channel is formed under the base of the brain which is called the circle of Willis.

The anterior cerebral artery supplies the cortex covering the mesial surface of the hemisphere from the frontal pole to the parieto-occipital fissure. This area includes the motor and sensory representation of the leg. The corpus callosum is also included. This artery further supplies the anterior part of the superior frontal convolution and the inferior surface of the frontal lobe. It sends penetrating branches into the anterior limb of the internal capsule and the anterior portions of the lenticular and caudate nuclei. Thrombosis of the cortical branches of this artery causes paralysis with spasticity of the contralateral leg, with or without cortical anesthesia. In many cases some degree of motor apraxia may be demonstrated as a result of softening of the corpus callosum. You are probably not familiar with the term apraxia. It may be defined as an

inability to perform purposive movements in the absence of paralysis, incoordination or dementia. Regardless of the side of the lesion, the apraxia is always in the left arm, or, more properly, in the subordinate arm. In some cases the patient's hand will always grasp objects placed in it, in such a way that it is difficult to relax the grasp. This is termed forced grasping. It has been shown by Walshe that this is due to a stretch reflex and is associated with lesions in the superior frontal convolution. It is always found on the side contralateral to the lesion. If the penetrating branches of the anterior cerebral artery are occluded, we may have hemiplegia on the opposite side.

The middle cerebral artery supplies the entire lateral surface of the hemisphere except for the anterior part of the superior frontal convolution and the inferior temporal and temporo-occipital gyri. It also sends penetrating branches which supply the internal capsule except for the anterior limb and the posterior parts of the lenticular and caudate nuclei. Thrombosis of the cortical branches may cause paralysis with spasticity of the contralateral arm and side of face when the precentral convolution is involved, cortical anesthesia confined to the arm when the postcentral convolution is softened and hemianopia when the optic radiation is involved in its passage through the temporal lobe. When the lesion is in the left hemisphere, in right-handed subjects, there may be either motor aphasia, sensory aphasia or both. Aphasia is a disorder of speech comparable to apraxia. In motor aphasia the ability to express oneself is chiefly affected and in sensory aphasia it is the receptive functions which are chiefly disturbed. In general, lesions lying anteriorly in the inferior frontal convolution are most apt to interfere with motor speech and lesions lying posteriorly in the superior temporal and inferior parietal lobes are most frequently associated with sensory aphasia. Bilateral apraxia may also occur when the cortex is involved in the region of the angular and supra-marginal gyri. If the penetrating branches are occluded, there will be complete hemiplegia, hemianesthesia, and hemianopia. Complete occlusion of the artery is almost always fatal within a short time for a very large part of the hemisphere is softened. The posterior cerebral artery supplies the occipital lobe,

the inferior surface of the temporal lobe, most of the thalamus and the midbrain. Thrombosis of the cortical branches of the posterior cerebral artery causes hemianopia and, if the lesion is on the left, alexia or inability to read. Occlusion of the penetrating branches may cause the classical thalamic syndrome of Dejerine and Roussy. Thrombosis of the small branches supplying the midbrain may cause a variety of symptoms including Weber's and Benedict's syndromes and cerebellar ataxia.

Thrombosis of the basilar artery is probably incompatible with life, but several interesting syndromes result from occlusion of branches of this artery. Softenings are found in the pons which cause hemiplegia on the opposite side and often homolateral paralysis of the sixth or seventh nerve. Cerebellar ataxia may result from injury to the brachium pontis.

Occlusion of the vertebral artery causes contralateral hemiplegia without involvement of the face and analgesia as well as thermanesthesia over the homolateral half of the face. Occlusion of one of its branches, namely the posterior inferior cerebellar artery, causes a very rich and interesting syndrome. There is paralysis of the homolateral side of the soft palate and larynx, anesthesia and thermanesthesia over the homolateral side of the face, analgesia as well as thermanesthesia over the contralateral side of the body below the face, cerebellar ataxia of the homolateral arm, nystagmus, vertigo and falling to the same side, and sometimes, myosis of the homolateral pupil and drooping of the homolateral eyelid. These symptoms are due to a softening in the lateral part of the medulla involving the nucleus ambiguus, the descending roots of the fifth and vestibular nuclei, the restiform body and the spinothalamic tract.

The treatment of thrombosis of the cerebral arteries is very unsatisfactory. Once the damage has been done it cannot be repaired. We are therefore forced to employ merely symptomatic therapy. During the stage of unconsciousness, we must support the circulation, administer proper amount of fluids and care for the bladder properly. Convulsions may be controlled by luminal or other sedatives. During convalescence, hemiplegia patients should have massage and passive movements to prevent contractures of the muscles and changes

in the joints. Later, they should have exercises and in certain cases orthopedic operations are indicated to prevent or cure deformities. If syphilis is present, or any other disease for which we have effective treatment, proper remedies must be applied, but we should not expect to modify the patient's symptoms by this means. At most, we may hope to prevent further damage to the nervous system.

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## CLINIC OF DR. MAXWELL M. WINTROBE

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#### THE APPLICATION AND INTERPRETATION OF THE BLOOD SEDIMENTATION TEST IN CLINICAL MEDICINE

IN little more than a decade the blood sedimentation test has attained widespread use. For this there are two reasons. One is the simplicity of the test; the other is its applicability to all phases of medicine.

The principle of the test is extremely simple. The blood is essentially a suspension of corpuscles in plasma. For the sedimentation test, blood is mixed with an anticoagulant, and the stability of the suspension is measured by putting some blood into a narrow tube which stands in a vertical position. The sedimentation of the red corpuscles can then be observed.

Although Fåhræus, a Swede, is responsible for the introduction of the sedimentation test into modern medicine, it is in a sense as old as the theory of the four humors. When blood was withdrawn from a healthy person, it was observed that it clotted and formed two portions, the serum and the clot. On the other hand, when blood was withdrawn from a diseased person, sedimentation being more rapid, separation of several layers occurred before clotting permitted no further change to take place. In this blood, four portions could be distinguished: (1) the uppermost yellowish fluid, formed by the blood serum ("cholera" or "yellow bile"); (2) a grayish-white layer of fibrin in the upper portion of the clot ("phlegma" or "mucus"); (3) a bright red layer made up chiefly of red corpuscles ("sanguis"); and (4) a dark red, almost black portion made up of red corpuscles deprived of oxygen ("melancholia" or "black bile"). In the medical philosophy of the ancient Greeks, ill health was thought to be due to the failure

of these four "humors" to mix. In the medical thought of later years the phlegma received chief attention and as the "crusta inflammatoria," "buffy coat" or "size" was thought to be the cause of disease. It was to rid the body of this supposedly harmful substance that venesection was performed.

Fåhræus' discovery of the value of the sedimentation test was quite accidental. In his search for an early test for pregnancy he found that the rate of sedimentation of the red corpuscles is increased not only in pregnancy but also in many diseases.

#### THE NATURE OF THE SEDIMENTATION PHENOMENON

Little is known about the true nature of the sedimentation phenomenon. Fåhræus pointed out that the suspension stability of the blood is determined by the radius of the suspended particles. Variations in the latter depend on differences in the degree of aggregation of the red corpuscles, with resulting formation of larger or smaller particles. In bloods in which sedimentation is rapid large aggregates are formed.

The cause of the increased aggregation or rouleaux formation of the corpuscles is not known. It appears to be some factor present chiefly in the plasma, for sedimentation is more rapid in plasma than in serum. There is a close correlation between the quantity of plasma fibrinogen and sedimentation rate, and there is some correlation between the amount of plasma globulin and the rate of sedimentation. Yet it is not correct to assume, as many writers have done, that the increased rate is therefore *due* to increases in plasma fibrinogen or globulin. The real causative factor has not yet been demonstrated.

#### METHODS FOR DETERMINING SEDIMENTATION RATE

Numerous methods have been devised for determination of sedimentation rate. Actually these are all modifications of two principal methods. The blood, to which an anticoagulant has been added, is placed in a narrow tube which is fixed in a vertical position. Then either the *time* required for the upper level of sedimenting corpuscles to fall a specified distance is measured (Linzenmeyer method), or the *distance* the corpuscles fall in a specified interval of time is noted (Westergren

method). The latter method is more generally used because it is so simple to fill the sedimentation tube and then to pay no further attention to it until the time chosen to read it has elapsed.

Some investigators recommend that readings be made at short, usually five-minute, intervals. When this is done and the readings are recorded on a chart, every variation from

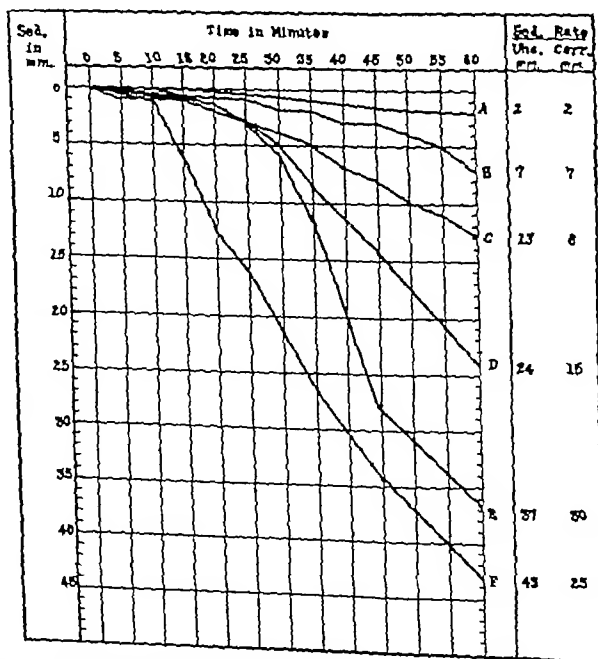


Fig. 107.—Sedimentation curves in the normal and in various disorders: A, normal; B, mild tonsillitis; C, mitral insufficiency without active rheumatic infection; D, chronic bilateral salpingitis and endocervicitis; E, bronchitis and bronchiectasis; F, acute pharyngitis, laryngitis and bronchitis. Both the "corrected" and "uncorrected" sedimentation rates are recorded in the last column.

an almost horizontal line to one which quickly falls in a vertical direction, may be encountered (Fig. 107). It can then be observed that in the process of sedimentation there are three phases: namely: (1) a preliminary period during which aggregation of the red corpuscles takes place, (2) a period of rapid fall, and finally (3) the phase of packing when the corpuscular masses, piling on one another, slow up the rate of sedimentation.

It is the phase of rapid fall which is thought to be of chief significance in the sedimentation test and for this reason charting of the changes which occur at five- or ten-minute intervals has been recommended. Actually, however, the distance which the corpuscles have fallen at the end of one hour is accounted for chiefly by this phase of rapid fall. Consequently, in the opinion of most workers, it is quite adequate to make only one reading, at the end of one hour. By doing this, the simplicity of the sedimentation test is preserved and yet adequate information is gained.

In the interpretation of the sedimentation test it is important to make certain that the test has been properly carried out, because a number of simple variations from the standard technic may cause delay or increase in the rate of fall of the corpuscles. Thus, if an excess of anticoagulant is used, the rate may be delayed. If the tube is allowed to stand even at an angle of 87 degrees rather than 90 degrees, the speed of sedimentation is markedly accelerated. It is also important to use tubes of uniform bore and length. Again, blood should be used for the sedimentation test within four hours of its withdrawal from the patient, as otherwise the rate may be less than that in freshly drawn blood. Furthermore, excessive cold will slow sedimentation while heat causes acceleration.

In order to ensure uniformity of results, we follow a standardized technic<sup>11</sup> using the hematocrit devised by the writer as the sedimentation tube (Fig. 108).

"1. Five cc. of venous blood is collected by means of a dry syringe and needle and mixed in a small bottle containing 4 mg. solid potassium oxalate and 6 mg. solid ammonium oxalate. This concentration of oxalate does not alter the sedimentation rate as compared with that of blood collected in heparin. Less than 1 cc. of blood is needed for the sedimentation test. The remainder can be used for other blood examinations.

"2. The blood so collected should be used for the determination of sedimentation rate within four hours of its time of collection. Further delay may be associated with increased suspension stability of the blood.

"3. The hematocrit is filled with blood to the 10 cm. mark.



The upper level of sedimenting corpuscles may be read at frequent intervals, or more simply, a single reading may be made at the end of one hour.

"4. Since sedimentation rate increases with increasing temperature, the sedimentation test should be carried out at a temperature not less than  $22^{\circ}$  nor greater than  $27^{\circ}$  C. Within this range variations resulting from differences in tem-

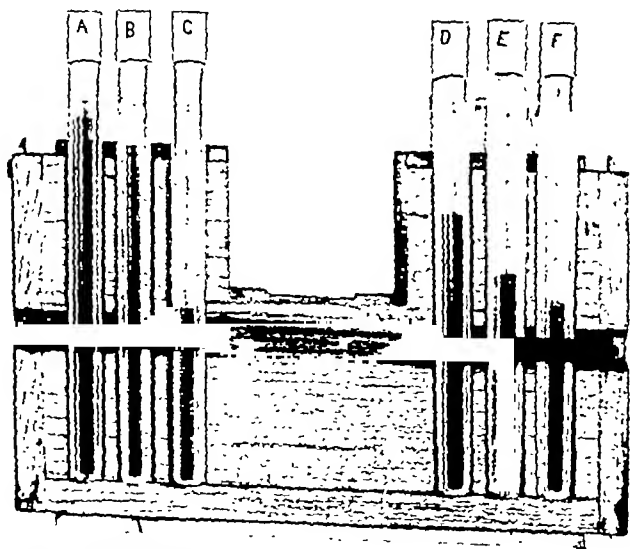


Fig 108.—Sedimentation of blood in hematocrit. A, Sedimentation of the blood of a normal male adult at the end of one hour; B, sedimentation of the blood of a normal female; C, the same sample of blood as in B, following centrifugation to secure complete packing of corpuscles; D, E and F represent the blood of 3 patients with slight, moderate, and marked increases in sedimentation velocity (Wintrobe, *International Clin.*, J. B. Lippincott Co., 1936, vol II, 46th series, p. 34.)

perature are small. If the blood used has previously been kept in a refrigerator it should first be permitted to attain the above temperature before being used.

"5. The hematocrit should be kept in an exact vertical position during the sedimentation of the blood corpuscles, for when the instrument stands at an angle of even  $3^{\circ}$  from the vertical, significant acceleration of sedimentation takes place.

"6. After sedimentation rate has been determined, the

hematocrit containing the blood should be centrifugalized and volume of packed red cells determined. The sedimentation rate may then be corrected for alterations due to anemia."

It has been repeatedly shown that variations in the quantity of sedimenting red corpuscles cause differences in sedimen-

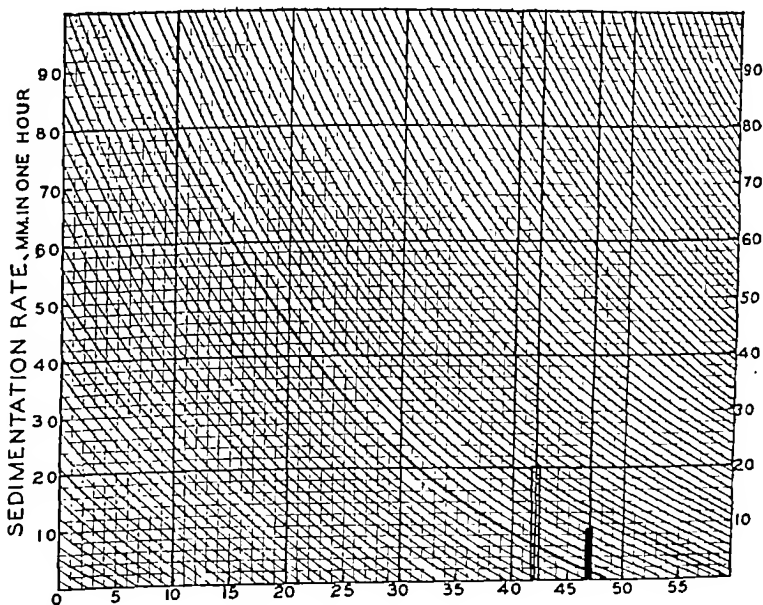


Fig. 109.—The logarithmic curve on which this chart is based is heavily outlined. The mean normal volume of packed red cells for men (47 cc.) and for women (42 cc.) are also heavily outlined and the range of normal sedimentation is represented by solid and open columns for each sex, respectively. For correcting sedimentation rate, find on the chart the horizontal line corresponding to the sedimentation rate for the patient; find also the vertical line corresponding to the volume of packed red cells in the patient's blood. Select the curve lying nearest to the point of junction of the horizontal and the vertical line and follow this curve to the normal line for the sex of the patient. The horizontal line corresponding to this last point of juncture gives the corrected sedimentation rate. A simpler method of correction is to correct all values to the volume of packed red cells normal for the male (47 cc.). Thus a single standard of normal can be used for both sexes. See text. (Wintrobe and Landsberg in *Amer. Jour. Med. Sci.*, 189: 102 [Jan.], 1935)

tation rate. A decrease in their number, as in anemia, permits a more rapid rate of fall, whereas when they are increased above the normal, practically no sedimentation occurs. Such alterations in sedimentation rate due to differences in the

quantity of corpuscles may be allowed for by the use of the chart shown in Fig. 109. .

There are several reasons why the hematocrit should be used for the sedimentation test. The chief one is that the quantity of corpuscles may easily be determined in the same tube by simply centrifugalizing (3000 revolutions per minute, for thirty minutes) after sedimentation has been recorded. As a routine procedure this is useful not only in simplifying the correction of sedimentation rate, but it is a quick and accurate means of discovering whether the patient has anemia or polycythemia. Furthermore, from the thickness of the layer of leukocytes and platelets which is found above the layer of packed red corpuscles, one may gauge roughly the quantity of these corpuscles in the blood. Finally, the icterus index may be measured by comparing the color of the plasma in the hematocrit with the color of a series of tubes containing potassium dichromate solution in various dilutions.<sup>9</sup>

In infants and young children, when venipuncture is not practical, a modification of the above method may be employed. The heel or finger is punctured deeply enough to secure a free flow of blood. With a capillary pipet blood is transferred quickly in successive small amounts to a small test tube containing approximately one-tenth the amount of oxalate mixture used for 5 cc. venous blood. Thorough mixing of blood and anticoagulant must be secured. After a little more than 0.5 cc. of blood has been obtained, it is transferred to the hematocrit, which is filled only half way. Sedimentation is then recorded in the usual manner, following which the blood is centrifugalized. To obtain the volume of packed red cells per 100 cc. of blood, the reading must, of course, be multiplied by two.

#### NORMAL SEDIMENTATION RATE. PHYSIOLOGIC VARIATIONS

The normal sedimentation rate differs according to the method used. It is therefore essential that a standard procedure be followed and the normal for the method employed be known.

In *health* a slight interindividual variation in sedimentation rate occurs, and there is also a distinct difference in rate between the sexes. Thus, when the technic described was em-

ployed, the sedimentation rate in healthy men averaged 3.7 mm. at the end of one hour (0 to 6.5 mm. in 86 per cent of the subjects) while in healthy women it averaged 9.6 mm. (0 to 15 mm. in 86 per cent). This difference, however, is largely accounted for by the quantitative difference in corpuscles in the blood of men and women. When these sedimentation rates in 136 men and in 100 women were "corrected" to a volume of packed red cells of 47 cc. per 100 cc. of blood, the sedimentation rate in 72 per cent of the men and women ranged between 0 and 6 mm. at the end of one hour, and in an additional 16 per cent, it was 7 to 10 mm. These values may be considered the limits of normal.

As has already been mentioned, sedimentation is accelerated during *pregnancy*. From about the tenth or twelfth week there is usually a gradual increase in rate which does not return to normal until the third or fourth week postpartum. A slight fluctuation of the rate of sedimentation occurs in relation to the menstrual cycle, but the changes are so small that, from a clinical standpoint, they are of no significance. Other factors, such as the ingestion of food, or short violent exercise, are of no importance.

#### VARIATIONS IN SEDIMENTATION RATE IN DISEASE

Methods for the determination of sedimentation rates and the variations under physiologic conditions have been discussed in some detail because, unless the technician performing the test and the physician interpreting the results are fully cognizant of these details, important errors may be introduced and the results in consequence become misleading. When the method is understood, however, the test becomes an extremely valuable aid in almost all phases of clinical medicine.

In the interpretation of the sedimentation test it is essential to bear in mind that it is a nonspecific reaction which may be compared with the temperature chart, the pulse rate and the leukocyte count, in that it gives information of a general character. It is in fact less specific than the leukocyte count when the differential examination of the white corpuscles is included under the latter head, for then the leukocyte count may offer a clue to the nature of the disease.

It may be asked what purpose there is in the sedimentation

test if it affords information of the same type as the temperature and pulse record and the leukocyte count. In answer it may be pointed out that in many disorders and even in certain stages of febrile diseases, there may be no fever or tachycardia and the leukocyte and differential counts may be essentially normal; yet in many of these instances the sedimentation rate may be increased. The sedimentation test is, thus, complementary to these valuable clinical tools. Like them it is a *measure of the presence and intensity of morbid processes within the body.*

Sometimes an increased sedimentation rate is found and nothing can be discovered to explain this increase. So little is still understood about the exact nature of the sedimentation reaction that a complete definition of the circumstances under which alterations in sedimentation rate may be expected to occur cannot be given. Yet, if the sedimentation rate in any patient is found repeatedly to be increased, the careful physician will seek to discover the cause.

The sedimentation rate is increased in all *acute general infections*. The degree of increase tends to parallel the severity of the infection. Although an accelerated rate generally does not appear as soon as elevation of temperature, the abnormal rate subsides more slowly and for this reason it may serve as a guide to the condition of the morbid process after fever and tachycardia have disappeared. When complications develop, the sedimentation rate is further increased and this fact may serve to indicate the onset of a complication before its nature and site have been determined. In *localized acute inflammatory conditions*, variations in sedimentation rate depend on the nature and severity of the morbid process. In *simple catarrhal inflammation*, such as acute catarrhal appendicitis, simple rhinitis and bronchitis, the sedimentation rate tends to be normal whereas in *localized acute suppurations*, such as pelvic inflammatory disease, suppurative mastoiditis or sinusitis, there is a pronounced acceleration of sedimentation. In *chronic localized infections* the rate varies with the extent and nature of the infection, normal values often being found in chronic tonsillitis, whereas increased rates occur in chronic bronchitis, tuberculosis, syphilis, nephritis and liver abscess. Generally speaking, sedimentation rate tends to be normal in

uninfected benign *new growths* whereas it may be increased when a malignant tumor is present. The latter, however, is not necessarily the case and the factors which probably determine whether the sedimentation rate is accelerated or not include the anatomic character of the growth, its vascularity, the tendency to break down, the degree of resorption of tumor tissue, the degree of reactive inflammation, and the location as well as the presence of metastases.<sup>4</sup>

### SEDIMENTATION RATES IN VARIOUS DISORDERS

The sedimentation reaction has been demonstrated to be of particular value in following the course of a number of disorders. It will be of interest to discuss these in detail for they illustrate the peculiar advantages of this test.

That the sedimentation test is extremely valuable in *phthisiology* is attested by numerous reports. In pulmonary tuberculosis, variations in sedimentation rate reflect the intensity of the morbid process more accurately than the pulse, temperature, weight, sputum, symptoms or physical signs. At the Trudeau Sanatorium<sup>5</sup> it was found that in some instances an increase in rate gave warning of relapses even before new shadows were found in the roentgenogram. No better claim for the test than this can be made, for the value of the roentgenogram as an index of the condition of the tuberculous patient is well established. When one considers the expensiveness of roentgenography and the difficulties sometimes encountered in interpretation, as compared with the simplicity of the sedimentation test, the importance of the latter becomes apparent. It does not, of course, offer any evidence regarding the extensiveness of the tuberculous lesion. The sedimentation reaction indicates the intensity and activity of the inflammatory process. In extensive and yet quiescent fibrotic lesions, sedimentation is less than in limited tuberculous processes with marked tissue disintegration.

The sedimentation test is favored by some investigators even in comparison with the various leukocytic indices. The value of the latter depends in large measure on the ability and interest of the observer. Differential leukocyte counts performed in a cursory manner by persons with inadequate train-

ing are of little value. Here again the simplicity of the sedimentation test gives it an important advantage.

In patients who are not under constant observation, the sedimentation test is especially valuable when repeated at regular intervals. Again, it is important in those receiving pneumothorax therapy for here collapse of the lung makes physical signs and roentgenograms of less value than usual.

A few observers have reported the finding of normal sedimentation rates in the presence of active tuberculous infection. Most workers will agree, however, that such a finding is extremely rare and usually represents a technical error. At the same time it must be pointed out that in severely cachectic stages of tuberculosis, the sedimentation rate has occasionally been found to be normal, or at least slower than earlier in the disease.

In the study of *rheumatic fever*, the sedimentation test is gaining an important place. Its value is found particularly in rheumatic carditis, where it is regularly accelerated. Except when associated with congestive heart failure, a decreasing rate nearly always reflects diminishing activity of the rheumatic process and as an index of this the sedimentation reaction is much more valuable than the temperature, pulse rate or leukocyte count. It has been found that an increasing rate presages clinical exacerbation and many clinicians now permit no activity on the part of the patient until the sedimentation rate has returned to normal.

In *acute cardiac infarction* and in syphilitic aortitis the sedimentation rate is accelerated, whereas in angina pectoris and hypertensive heart disease the rate is normal. In cases of cardiac infarction the test is a valuable guide in deciding upon the duration of rest because in this condition, as in rheumatic carditis, an accelerated rate may be the only evidence of activity of the morbid process.

Rheumatoid, tuberculous and gonorrheal arthritis, and other inflammatory *diseases of bones and joints* are associated with accelerated sedimentation rates, whereas in hypertrophic or osteo-arthritis, the rate is usually normal. For this reason, the test has been used in aiding the differentiation of rheumatoid from osteo-arthritis. In this respect, however, it has not always been found reliable.

In *gynecologic practice*, the sedimentation test has achieved a position of great usefulness. The principles involving its use are the same as those already outlined. Uncomplicated benign tumors, such as fibromyomata or ovarian cysts, mild infections or quiescent inflammatory disease, are associated with no increase in sedimentation rate, whereas when there is active inflammatory disease the rate is accelerated. Degeneration of benign tumors, twisting of the pedicle of an ovarian cyst, and often malignant disease, are associated with rapid rates.

Since the sedimentation rate is not usually increased in pregnancy until the tenth or twelfth week, the test can be used as an aid in differential diagnosis and as an indication of the presence of complications in cases of abortion and ectopic pregnancy. Retention of uninfected products of conception, hemorrhage or infection causes acceleration of various degrees.

In acute and subacute salpingitis the rate is greatly increased whereas in acute appendicitis only slight increases usually occur. Subsidence of pelvic infection is associated with return of sedimentation rate toward normal. Many gynecologists have found this fact a useful guide in indicating a favorable time for elective operations.

In aiding the study of *gastro-intestinal disorders*, the sedimentation test has not as yet attained the general application that it enjoys in the fields already discussed. It has been used by some clinicians, however, to facilitate the differentiation of functional from organic disturbances, benign ulceration from malignant, simple diarrhea from enteritis and colitis. The usefulness of the test in these respects is limited. As has already been pointed out, an increased sedimentation rate is not always associated with malignancy and whether or not the rate is accelerated in inflammatory disorders depends on the severity of the inflammatory process. It is of interest to note that in parenchymatous diseases of the liver, sedimentation rate may be actually less than normal. This has been explained as the result of failure to form fibrinogen which, as already mentioned, is closely related to the sedimentation reaction.

Undoubtedly one of the most important uses of the sedimentation test is in *calling attention to the presence of more or less occult diseases*. As a routine procedure to be performed



as part of the general examination of a patient, the test is very valuable, for an accelerated rate may not infrequently be the sole evidence of the presence of disease and serves in this way as an indication of the necessity for further study of the patient.

When the sedimentation test is carried out in the manner here described and the other steps in the use of the hematocrit performed, one obtains, as the result of a minimal expenditure of time and effort, information regarding not only sedimentation rate but also concerning the presence or not of anemia, leukocytosis and icterus.

When the sedimentation test is used as a routine procedure in the examination of a patient, it must not be assumed that a normal rate necessarily signifies the absence of disease. Occasionally it is found, although it is very rare, that the rate is normal in spite of the presence of organic disease. Thus among 444 cases at the Diagnostic Clinic of the Johns Hopkins Hospital in which the corrected sedimentation rate was 10 mm. or less, manifest organic disease was found in 8 instances. In one case of continued fever of undetermined origin the sedimentation was 0 at the end of one hour. In two cases of chronic nephritis with marked renal insufficiency the rate was 0 and 1 mm., respectively, while in a patient who had active pulmonary tuberculosis as well as hay fever, it was 7 mm. Again, in a patient convalescing from amebiasis who still had some elevation of temperature, the rate was 8 mm.

Three of these 8 cases illustrated the importance of recording the uncorrected as well as the corrected sedimentation rate. One patient had acute pyelitis with hydronephrosis, another had carcinoma of the descending colon and the third had cystitis, pyelitis and renal insufficiency. The corrected rates were practically normal (8, 9 and 10 mm., respectively), whereas the uncorrected values were markedly accelerated (37, 30 and 39 mm., respectively). In these instances the accelerated rates were masked by the correction for anemia.

A study at the Henry Phipps Institute in Philadelphia<sup>2</sup> stresses the importance of paying due regard to sedimentation rates which are found to be accelerated although the general examination of the patient is negative. In 177 of 328 individuals who, after routine examination, had been considered

healthy or suffering from only trivial ailments, the sedimentation rate was increased. Reexamination of these patients revealed basal nontuberculous infiltration of the lungs in 96, "latent" apical tuberculosis in 32, positive Wassermann reactions in 35, pelvic inflammatory disease in 5, and possible carcinoma of the lung in 1. Only in 8 cases was there no abnormality found on reexamination.

Criticism of the sedimentation test arises from a failure to understand the nature of the reaction and, as with all laboratory procedures, from failure to appreciate the importance of attention to what may appear to be trivial technical details. It must be emphasized that slight alterations from the standard technic may cause great differences in results. As has been pointed out, "correction" for anemia may occasionally be misleading. While correction should be made, the uncorrected rate and the hematocrit reading should be recorded as well as the corrected sedimentation rate. Again, it may be repeated that normal sedimentation velocity may occasionally be found in the presence of disease. Finally, it must be stressed that the reaction is a nonspecific one referable to no particular disease and only indirectly of value in differential diagnosis.

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## CLINIC OF DR. THOMAS A. C. RENNIE

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### RECOGNITION AND MANAGEMENT OF THE NEUROTIC PATIENT

WHEN do we consider the complaint of a patient a "nervous" one? What facts give us the right to speak of a neurosis? Most physicians recognize a vast group of individuals who complain regularly and monotonously and about whom they are never able to find sufficient physical findings to account for the multiple complaints. We might, therefore, speak of the neurosis as a complaint disorder, and by conservative estimate, 40 per cent of any general practice is made up of such complainers. The "neurosis" or "psycho-neurosis" is a misnomer implying, from the days of Weir-Mitchell and rest-cure therapy, a fundamental weakness of the neuron system. Today we know that the neuron is unimpaired, and that these conditions represent personality difficulties often predicated upon inability of the individual to stand the stresses and strains of his life; in brief, one who has failed in achieving essential satisfaction out of life.

These are individuals who come to the office regularly or make the rounds of doctors, each time reiterating their multiple discomforts, often presenting at each visit new and variable ones. Some of these are clearly "mental," such as compulsions for handwashing; phobias and fears of germs, dirt, homicidal possibilities, etc., recognized by the person as "mental" and thoroughly illogical, but against which he has no defense. More often, the patient feels no responsibility for his symptoms, and complains of general nervousness, tearfulness, trembling, "jitters," tremors, or hypochondriacal insistence on aches and pains, multiple and diffuse, affecting any or

all organs. A typical hypochondriac, with his marked over-awareness of bodily functions and sensations, produces symptoms for each system review of the doctor's history, or incriminates a special organ such as head, heart, stomach; expressed as inordinate suffering, multiple and shifting areas of discomfort, and dire evidence of cancer, ulcer, heart disease. Or the neurasthenic is chronically fatigued, working out his disappointments in exhaustion, irritability and insomnia, which keeps him in bed, unable to face the tasks of daily life. The hysteric dramatically simulates standard diseases with numbness, anesthetics, palsies, blindness, aphonia; manifested in pseudoneurological ways and atypical sensory disturbances. A third group, complaining of anxiety symptoms in palpitations, sweating, globus, sense of suffocation and fear of death; tension in dizziness and head sensations, nausea, vomiting, diarrhea, constipation; or motor neuroses as tics of face and head, jerks, spasms, occupational (writer's, telegrapher's) cramps, are usually convinced they have a real disease but may spontaneously recognize the rôle of anxiety, worry, disappointment, and anticipation in exacerbating their symptoms. Occasionally, a patient spontaneously recognizes the true nature of his symptoms, thus speaking of "nervous" stomach, heart, headache, "nervous" exhaustion, vomiting, or diarrhea, "emotional" fatigue, worry and insomnia, etc.

When any such patient does directly or inadvertently mention nervousness, worry, discouragement, apprehension, or "nervous breakdown," he is all too quickly labeled "neurotic," given bromide, and often summarily dismissed as hopeless or, at best, hardly worthy of a busy practitioner's time. Or he is presented with vague terms, meaningless to him, and runs the risk of further complicating his problems with ill-digested terminology, or a note of pessimism. He may even meet brusque dismissal with a statement that his imagination alone is at fault. Such is not true. His various symptoms are painfully real to him, his distress not alleviated by advice to forget himself, which he is equally unable to do.

The physician himself is apt to be equally puzzled. Concepts such as irritable heart, effort syndrome, neurocirculatory asthenia add little to his understanding. He may hide behind suspicion of malingering or subterfuge. Actually he is dealing

with a special type of personality reacting to life experiences as precipitating factors. Tradition blames overwork, desire to attract attention or arouse sympathy, to "escape" responsibility. We need to know that functional changes in essentially normal organs can bring about discomforts and disturbing sensations under states of worry, anxiety, fear. Or protracted states of tension, irritability, and anxiety may mound into states or *attacks* of acute visceral upheaval with tachycardia, choking, sweating, dizziness, and conviction of imminent death. Frustraneous overstimulation, especially sexual and emotional, without adequate periods of satisfaction and relaxation may contribute. Life problems, such as limited finances, work maladjustment, infidelity, worry over religion, family, pregnancy, contraceptive issues, may create states of insecurity which set off overactivity or irregularity in essentially normal organs. Disappointment and traditional sex lore fears, masturbation worries and coitus interruptus may give rise to complaints of profound exhaustion, poor concentration, backache, etc. Or, as in hysteria and obsessions, we may deal with past experiences, *forgotten* ("repressed"), *dissociated* (cut off), and *converted* into fits, pseudoneurological palsies or obsessive doubts, rituals, fears. Freudian psychoanalysis puts the interpretation on mechanisms, repression of unacceptable urges or fancies, particularly related to childhood and infantile sexuality, the "Oedipus" and "inferiority" complexes, etc. We do best to remember that unhappy experiences and memories, anticipations, life and situational strains all conspire to render certain temperaments disabled or neurotic. It is necessary to remember that we deal with a special type of personality make-up in whom "body protests" represent the unbearable strain of life situations.

Any of these conditions may develop accompanying or reactive states of discouragement or depression, and sometimes represent precursors to more serious and sweeping mental disturbances, such as schizophrenic developments and depressive psychoses. Not infrequently, the discomforts lead the individual to seek relief in drinking. Such individuals, being dependent types, may become alcoholics or drug addicts, sometimes as a result of the physician's unwise use of sedatives, hypnotics, and tonics.

**What Is the Neurotic Type?**—The neurotic constitution is difficult to define with exactitude. Difficulties beginning in infancy are frequent. One finds evidence of early instability in the so-called “neurotic” or “neuropathic” traits, namely, excessive timidity, shyness, submissiveness, fears, nightmares, explosive temper, enuresis, nail biting, vasomotor instability, protein sensitivity, allergy, hives, eczema, asthma. These conditions may exist in any social and intellectual level: both in precocious intellectual types and in retarded, feeble-minded individuals; or they may arise during adolescence, which is the decisive period in the formation of the adult personality, particularly with the development of emotional instability, over-conscientiousness, rigid ethical and moral standards, tendencies to anticipate troubles, “to cross bridges before coming to them”; and with hypersensitiveness and aloofness, feelings of inadequacy, and a sense of the individual’s isolation from his group. Or there may be precocious or diminished or abnormal sexuality with its tendency to increasing secretiveness, and satisfaction of cravings in imagination. Thus we find adults who in spite of apparent outward calm are characteristically shy, timid, hesitating, indecisive, easily led, tending to dwell and elaborate on past experiences, anticipating with dread the changes of the future.

This temperament is one poorly equipped to meet the issues of life. Thus we find them responding in any of the above varieties of ways when life situations become troublesome or insistent. Almost any person will react with symptoms if inordinate burdens are placed on him. The neurotic reacts sooner and to lesser burdens. He is poorly equipped, physically and temperamentally, to meet the complexities of adult life.

In physical make-up, too, they are apt to be loosely organized. We find them often as underweight, asthenic types, with visceroptosis, spastic constipation or colitis, requiring more sleep and rest than the average. We find excitable reflexes, unstable autonomic types, with labile pulse and hyperactive sympathetic nervous systems; easy blushing, dermatographia, circulatory and vasomotor instability; hypersensitive skin; menstrual dysfunctions; carbohydrate and water imbalance.



Such physical constitutions react violently to emotional upsets. Many of the neurotic symptoms represent essentially, then, the body protests of the personality faced with insecurity and inability to find satisfaction.

**Explanation of the Neurotic Conditions.**—What commonly lies back of such conditions? The answer is to be found only in an understanding of the personality and constitution and a complete record of the life events. Every personality is different and individual, and consists of its physiologic or biologic component, its particular emotional make-up, its intellectual assets and liabilities, and its special temperamental type. Some of these are inherent in the stock of the person, some are molded and determined by the life events from the moment of birth on. What we are results from the interplay of life experiences and happenings on the original constitutional stuff of which we are made. Every individual functions with certain drives and instincts, his particular quality of intelligence, his sexual rhythm and urges, his social and occupational needs and satisfactions, his religion, family and marital strivings, and all within a certain range made up of a sensible balance between work, play, rest and relaxation. In certain temperaments, any of these components may be subjected to strains impossible to endure with comfort. When that happens, we can get neurotic symptoms.

The exact stuff of the personality is fairly easy to evaluate by any physician sensitive to life problems, willing to listen for forty-five minutes to an account of the patient's life, and able to remain objective and free of personal embarrassment. A simple review with any patient will bring to a focus telling and dynamic facts. The early childhood, with or without its neurotic traits, gives an immediate picture of the essential constitution. The school record gives a clue as to the intellectual status: frequent school failures, or inability to get beyond eighth grade, are apt to be indicative of limited intellectual endowment. It is well to remember that the average adult has an intellectual capacity of approximately eighth-grade caliber. An intelligence test, if it is available, clinches this aspect of the personality. The record of success or failures in jobs gives a clue to the innate dependability and stability of the person and a clue to occupational strains. Every intelligence and tem-

perament has its level at which it works contentedly, beyond which it becomes uncomfortable. An account of the marital and sexual status may bring to light immediate topics of worry or concern, fear of pregnancies, sexual dissatisfaction or distaste, incompatibility between partners, masturbation worries, etc. The financial status and strains are easily evaluated. The degree of success or failure in making friends or the relationship to the family and broader community interests quickly brings out essential problems or lines of sensitiveness. An account of the parents, siblings, and relatives brings out liabilities in the stock.

**What Precipitating Factors Can Be at Fault?**—Any or all of these factors may be the important determinant of the particular psychoneurotic reaction. During such a review, precipitating factors will begin to assume their real importance, especially if their presence correlates in time with the development of the complaints. Such factors are often acute: operations, death in the family, accident, quarrels, fright, chance remark of physician, awareness of anxiety on the part of the physician; more often insidious and prolonged factors lead to a development of strain, tension, anxiety or worry which culminates in the patient's complaint. Irregularity of work, inadequate income, work under pressure, ambition beyond capacity, promotion and the fear of not making good, illness of relatives, religious conflicts, sex ruminations and conflicts, fear of death, conflicting medical statements or advice, and innumerable other life factors take their toll in undermining the patient's confidence and security, leaving him worried, apprehensive, discouraged and puzzled. Any of these states of mind may cause or enhance physical complaints and visceral participation. These are common facts which underlie most psychoneurotic reactions.

**How the Life Facts Work.**—Out of these life problems are produced the neurotic symptoms. Cannon has shown us the interrelation between fear and other emotions, and certain physiologic concomitants that go hand-in-hand. An emotional state is, after all, a physiologic state bringing automatically with it disturbing variations in any or all of our physiologic functions. Thus fear is a condition characterized as much by tachycardia, sweating, dilated pupils, interrupted

gastro-intestinal motility and secretion, adrenalin hypersecretion, and sweeping metabolic changes in metabolism, water balance, etc., as by a subjective awareness of insecurity or danger. In the same way, any emotion, whether it be worry, anxiety, strain, discouragement, or anticipation, carries with it its pattern of concomitant physiologic changes. In years gone by, under the influence of Descartes and Wundt, we spoke of the body-mind relationship or parallelism. Today, we say a human personality is made up of all these factors: a ceaseless interplay and flux between somatic and more specifically "mental" functioning.

**Obtaining the Human Facts.**—Personality and life facts are easy to obtain by any physician who can establish an attitude of confidence, understanding and willingness to deal with everyday human events. Formal history is not necessary. The following questions should prove helpful in eliciting essential components: what is your complaint? When and how did it develop? Were you worried at the time? What things concern or distress you? Were things going smoothly at home, at work, or with relatives or friends? Any quarrels, disappointments, shocks, or fright? What do you think causes your condition? Have you heard things about your illness that worry you? Any relatives or friends have a similar condition? Are you apprehensive about your future, or troubled by memories or past experiences?

Then one goes quickly through the items of a personal review: anything unusual in your childhood? How far did you go in school? Any failures? What jobs have you had? Are you happy in your present work, or are there difficulties? Are you happy in your marriage? How do you get along with husband or wife? Do the children worry you? Any difficulties with the sex part of your marriage? Do you want more children? Do anything to prevent pregnancy? If so, does it worry you? What methods? Any fear of pregnancy? Do sex relations lead to relaxation or unrest? Any worries about masturbation? Any financial problems? Does your religion give you concern? Describe your temperament. Are you moody, cheerful, friendly? Have you any hobbies? Do you enjoy movies, friends, athletics? Any tendency to nervousness in your family?

These human facts serve as the important material for the treatment of the neuroses.

**Treatment of the Neuroses.**—In discussing treatment, one must remember that it must be adjusted to the person and the condition. There are physicians who insist on a diagnosis and work from that basis. There are others who know how to listen and can create an atmosphere of trust. Some work essentially through talking; others think first of general hygiene and finding a level of comfort for their patients. Certain fundamental rules apply to all cases. Only if we accept the inter-related integration of "mental" and physical functioning are we in a position to help the psychoneurotic patient. There is no panacea. Many theories have been advanced for the understanding and therapy of such conditions. Older psychiatry concerned itself largely with the constitution and concept of inherent degeneracy. Later psychiatry emphasized malnutrition, chronic infection and metabolic disturbances, which latter even today has its exponent in the endocrinologically minded physician. Rest, eradication of foci of infection, colonic irrigation, dietary fads, gymnastics, and drugs have all had their day. Pharmacology has recently given us benzedrine as a specific type of stimulant. Psychoanalysis is time-consuming and cures by "talking out" the unconscious repressed memories and phantasies. Today we take from all this whatever seems to promise returns, but prefer a pluralistic working concept which never loses sight of the fact that a person has a life history and life story and that in the biography of the person, one finds facts whose bearing on these conditions cannot be ignored. Treatment, therefore, must be carried out with an open mind and willingness to utilize all avenues of approach.

Treatment begins with the first interview. The complaint has been obtained and its development, and the setting of the complaint has been clarified in an accurate chronologic account of the life situations at the time of onset. We have taken a little time to learn something of the patient's fundamental biologic make-up, his ability to stand strain, his intelligence and its limitations, and his special temperamental liabilities. This may be the first time the patient has had a chance to understand what really is happening inside him. Frequently

the mere chronologic accumulation of symptoms with life events brings with it the patient's own spontaneous realization of the way in which worries cause physical symptoms. This is what we mean by *insight*. The first step is to begin by *settling* for the patient the issue of the suspected organ, acquainting him with the results of examinations and convincing him that he is physically sound. Such an examination should be completed as soon as possible, in order not to undermine the patient's confidence by an impression of uncertainty on the physician's part. Unnecessary or purely investigative procedures may stir up doubts. It sometimes takes rather dramatic conversation and a show of authoritativeness to convince a patient. It is then *explained* to him that the findings are definite and that he has no organic disease; that these symptoms represent the participation of his body in the various emotional states which he has enumerated, and he is shown how the factors which have just been elicited play their rôle in producing the part-participation of the physiologic system. His cooperation must be enlisted in fighting the underlying emotional states. It is often gratifying to see how patients have been groping toward such an explanation in a spontaneous fashion. It is common to hear, "Why, I've known that all along. I knew it was just worry." Others are ashamed to admit that their personalities could get such a rise out of them. Sometimes, the patient must be *persuaded* to accept the real nature of his complaints. It is well, whenever possible, to interview a responsible member of the family, in the patient's presence, and give him the same understanding of the true causes and elicit his cooperation in management.

If the physician takes time to put over these concepts, it is surprising how quickly palpitations, weakness, etc., cease to spell for his patient mysterious and ominous warnings of disease or disaster. In fact, the symptoms achieve a certain respectable status, something tangible and common to most human nature, even the most normal varieties. We urge the patient to accept himself and his make-up as they are. To accept is to shoulder the burden of treatment for himself. Often a single such interview will bring about a real amelioration. When the patient returns, as he usually does, the physician has an opportunity to repeat the same explanation,

to offer another dose of reassurance and encouragement, and to give him a chance to ventilate new or additional old worries that have a bearing on the condition. Patients want to know how long treatment is likely to take. It is well to give no statement of *time*, as the human tendency is to check off the days in anticipation of the hour of cure. It is better to state frankly that one does not know, that the illness took time in developing, and that the reestablishment of self-confidence involves patience and time. To commit oneself to a time limit is to run the danger of losing the patient's confidence when the time limit has expired and the symptoms have not vanished.

Having achieved this much in the initial interview, we may then set out to meet the environmental and precipitating situation. When the patient is willing, we can accomplish a great deal in *reorganization* of his life. Where intelligence is low, and a job or school constitutes an unbearable strain, we recommend change, and even attempt to arrange such with the employer. In the same way, we may have to count on the cooperation of schools, and of relatives and friends. As a rule, we urge such patients to return to work, to *accept* the true nature of their complaints, to put up for the time being as well as they can with their distressing symptoms and to get back into the rush of life, or to return and face the troublesome situations. It is imperative to avoid medical terms, however vague, as they seldom connote to the patient what they do to the physician. Often it is impossible to modify situations such as limited finances, the care and burden of relatives. If this is impossible, we persuade the patient to *accept* the facts as they are, or to modify his attitude of conscientiousness or resentment toward them so that they become more acceptable.

Usually no one factor is at fault, but the condition represents a variety of difficulties, all of which may need modification. It may be necessary to *desensitize* the individual to his past experiences, giving him some concept of the prevalence of such events in human life. It may be necessary to give contraceptive advice or hygiene of normal sexuality, which takes the shame and fear away from masturbation, which teaches the wisdom of avoiding unnecessary sexual stimulation in fact or in fancy. The entire aim is to reestablish the patient's confidence in himself and in his physician, to discuss

his problems, however simple and trivial they may appear, in order to bring the relief which objectivating them often accomplishes.

Treatment of hysterical and obsessive conditions is more difficult. Strong positive suggestion of cure sometimes removes the hysterical symptom. Obsessive habits of thinking or behaving have to be deliberately broken up like adhesions, which is only possible with the patient's cooperation and sometimes only in the controlled environment of a hospital. Reassurance about phobias is important. Such patients rarely, if ever, carry out the suicidal or homicidal urges which they so fear. Lasting cure comes only with thorough analysis of the underlying dynamics, which brings the patient awareness of the essentially disturbing factors.

Treatment is not mere talking and listening. Every human being is entitled to some share of satisfactions. It may become necessary to *plan* his life for him to insure his getting maximum satisfaction. It is wise to give him a written schedule which provides for work and sleep, a sensible dietary program, rest, relaxation and play. Substitution of any hobby for idleness and self-preoccupation can be a real boon, just as deliberately giving up daydreaming may avoid unhealthy arousals. Many such a patient has found in gardening, in reading, in regular vacations, in study, in club or church life, or in athletics a real balance for a temperament which tends to be too self-centered. In addition, such a program helps to break up the actual preoccupation with sensations or problems. Any pain becomes worse the longer we think about it. We urge patients to deliberately put aside thoughts about their problems, and to find relief from them in activity.

Attention to the *physical condition* is important. Diet and insulin are effective in increasing weight. Constipation must be combated, preferably by diet, massage and exercise. Enemata should be discouraged; strong cathartics avoided.

The physician has no more useful armamentarium at his disposal for the production of physical relaxation than well-planned *hydrotherapy* and *exercise*. Prolonged soaking of an hour in a tub of water at  $99\frac{1}{2}^{\circ}$  F., or slightly over body temperature, at bedtime or twice a day, often means a real night's sleep and a letting down of the tension of the day. It is well

to avoid any medication, particularly sedatives. No amount of reassurance about the physical well-being can undo the undermining of the physician's words that a prescription can mean. One must strive for consistency. To pronounce an organ sound and then prescribe additional rest or modified activities, or a special diet, is to leave the patient with a serious doubt as to the original pronouncement. In spite of all advice, the general physician will probably resort to some sedatives because it seems his only way to hold his patient through a difficult time. If sedative is used, it should be accompanied by careful explanation that the medication is only a means of producing symptomatic and temporary relief; that it is an artificial means of easing painful symptoms or anxieties in order that he may ultimately correct the more fundamental attitudes, situations, or concepts leading to the insecurity with regard to himself. Barbitol, luminal, sedormid, dial and amytal are simple to prescribe, and effective. Sympathetic nervous system depressants and antispasmodics often bring real relief. Tincture of belladonna may relieve spastic gastrointestinal states. Ergotamine tartrate or gynergen in 1-mg. doses two or three times a day may be helpful in toning down too active a sympathetic nervous system.

It is rare that a psychoneurosis develops after thirty without there having been precursors of the reaction during previous life periods. The physician likely to succeed is the one humanly interested in his patient's story. The patient senses an attitude of understanding which no physician can feign. Any state of general nervousness, tension, anxiety, hypochondriasis, or neurasthenia can be adequately and successfully treated by the nonspecialist. Patience is necessary as well as the ability to sustain interest. One must not fail with reassurance and encouragement or become bored with the slowness of response. One must become sensitive to the events of his patient's lives, and learn to interpret and deal with them. In this, the old time practitioner was an intuitive artist, but without intuition and without art, one can acquire medical and human wisdom without sacrificing one's status as objective scientist.



## CLINIC OF DR. LESLIE N. GAY

### THE JOHNS HOPKINS MEDICAL SCHOOL

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#### A CLINIC TO EMPHASIZE THE CLOSE INTERDEPENDENCE BETWEEN INTERNAL MEDICINE AND ALLERGIC MANIFESTATIONS

IN his office today the diagnostician finds many clinical problems which are related to allergic manifestations. This has always been so; but during the past two decades our more definite knowledge of allergy has increased our ability to diagnose and treat these special problems. Allergy has become a term well known to the average intelligent layman probably because of the numerous popular articles which have appeared in the monthly periodicals, and for this reason opportunity to diagnose these diseases has increased. But the enthusiasm which greets a new phase in medicine sometimes swings the pendulum so far that judgment becomes faulty and for this reason a note of warning is sometimes necessary to remind us that *the obvious must not be overlooked* while we are searching for an explanation of our problem in the more obscure special fields of diagnosis. And so it happens that a clinic designed to point out the necessity of a better understanding of the general problems of medicine by the allergist and of the necessity for a better understanding of the problems of allergy by the internist and general practitioner is opportune at this time.

#### GROUP I

Case I.—J. S., a girl, aged four years, was brought to me first in June, 1933, with a history of eczema which had begun in infancy. From time to time it would spread over the entire body and was particularly irritating at the folds of the skin. Two years after the onset of her eczema, at the age of three years, she developed attacks of coughing with marked shortness of breath and a running nose. These attacks would last for from twenty-four to forty-eight hours, clearing up and recurring at irregular but frequent intervals throughout the year.

The physical examination was entirely negative; whereas the history definitely suggested an allergic eczema, an allergic rhinitis and an allergic bronchial asthma. Using the passive transfer technic of Prausnitz and Küstner<sup>1</sup> because of the age of the child, we found the patient to be markedly sensitive to the house dust with which she came in contact in her own home. All other tests with suspected protein extracts gave no reactions.

Specific treatment consisting of injections of an extract of dust obtained from the child's home was given and a most satisfactory improvement followed. The schedule of these injections was as follows:

## CHART 1

## TREATMENT SCHEDULE: HOUSE DUST

1. Treatment consisted of subcutaneous injections of dilutions of a specific house dust extract. The material was prepared by adding Coca's extracting fluid<sup>2</sup> to a given quantity of dust. This fluid was then decanted after three days, passed through a Berkefeld filter, cultured for sterility and diluted for treatment.

2. Treatment was given every three to four days.

Dosage: *Dilution 1:1000*

0.1 to 0.9 cc.  
(6 doses)

June 22 to July 6.

*Dilution 1:100*

0.1 to 0.9 cc.  
(6 doses)

July 6 to July 27.

*Dilution 1:10*

0.1 to 0.9 cc.  
(8 doses)

July 27 to August 30.

3. After 0.9 cc. of 1:10 dilution was reached this amount was given once each week for a period of six months. At the end of this time, the symptoms had entirely subsided and the injections were discontinued.

<sup>1</sup> The Prausnitz-Küstner technic consists of the injection of the serum, taken from an allergic suspect, into the skin of a known nonallergic recipient. This serum locally sensitizes the normal skin and after twenty-four hours specific allergens can be injected locally into the sensitized sites. The union of the allergen with the specific sensitizing reagents will produce a reaction similar to that which one can obtain by testing directly the allergic suspect if he is sensitive to the specific material.

<sup>2</sup> Coca's solution:

2.8 Gm. sodium carbonate.

5 Gm. sodium chloride

4 cc. 95 per cent phenol.

1000 cc. distilled water.

On January 27, 1936, the child's physician again consulted me because, in his opinion, the child had developed definite allergic manifestations referable to the gastro-intestinal tract. For the previous eighteen months while taking the above injections, she had been free from all respiratory symptoms. However, six months before the second consultation it was noted that there was a recurrence of nasal discharge, occasional sneezing and acute abdominal pain which came at any time of the day or night, either after eating or unrelated to food. There was also at times a definite rise in temperature, but on several occasions the temperature had been quite normal although pain was severe. With the last attack of acute abdominal pain, the week before I saw her, she had had a severe attack of asthma.

Physical examination showed a very well-nourished child—a great improvement in comparison with the condition existing on her first examination in 1933. There were no râles in the chest, but there was some mucous discharge from the nose. The abdomen was entirely negative except for slight generalized tenderness over both lower quadrants.

The intradermal food tests performed on the child were negative, but she now showed a definite reaction to *orris root* as well as to *dust*.

Blood morphology showed a slight secondary anemia but with no eosinophilia. Day and night specimens of urine during the period of examination showed scattered clumps of pus cells; catheterized specimens contained many pus cells and bacteria (*Bacillus coli*).

An acute pyelitis, rather than food allergy, was found to explain the gastro-intestinal symptoms in this child and by proper treatment the laborious diet regulation was avoided. The return of asthmatic manifestations, it is true, somewhat masked the picture, but these symptoms diminished when orris root powder was eliminated from her environment.

The patient was treated as one suffering from recurring attacks of pyelitis. Since August, 1936, she has been entirely free from symptoms, the urinary infection having been controlled by the simple measures used in the management of acute pyelitis.

Case II.—B. G., a girl, aged five years, was brought to us first in August, 1936, with a history of urticaria. The eruption was distributed all over the body, but was more annoying on the extremities than on the trunk. Associated with the urticaria there were crises of nausea, vomiting and generalized abdominal pain. There was occasional slight fever, as high as 99.6° F. These episodes had been recurring about once in two months for two years.

Examination showed a well-nourished child. An innocent appendix had been removed a year before she came to us. Her physician felt that she was having definite gastro-intestinal allergic reactions in conjunction with the urticaria. Physical examination was entirely negative. The blood morphology was normal and there was no eosinophilia. All intradermal protein tests were negative. Repeated urine examinations showed scattered pus cells in several catheterized specimens. During the examinations which were carried on rather

slowly because of the age of the child, she suddenly developed an extensive urticaria, a rise in temperature to 99.8° F. and acute generalized abdominal pain. During this episode a careful study of the urine was made and numerous clumps of pus cells were found in repeated catheterized specimens, the cultures showing the presence of *Bacillus coli*.

This case presents a striking example of the relationship between infection and urticaria. In a report by Fink and Gay, in 38 per cent of 170 patients who were suffering from urticaria the skin symptoms were found to be due to some obscure infection; and by the removal of the focus complete relief was obtained in 74 per cent. Such cases serve to emphasize the importance of a careful diagnostic survey before a snap diagnosis is made that the appendix is at fault or that some innocuous food is causing the mischief. This was an example, not of food allergy, but rather a reaction of the capillary bed to the absorption of toxic products associated with a chronic low-grade pyelitis.

## GROUP II

The possible association of mechanical factors with allergy must never be overlooked. The presence of a foreign body, as a possible explanation for the acute paroxysms of cough must always be thought of in patients suffering from asthma, especially before the age of twelve years, and the offender must either be localized or excluded. The patients belonging to a group now presented are in the third and sixth decades, however, and their symptoms were not secondary to aspirated foreign bodies; neither were they to be explained on the basis of allergy, in spite of the fact that the histories pointed to that special field.

**Case I.**—M., aged thirty-four years, first consulted us in March, 1933, complaining of violent and frequent sneezing spells during one year. Her sneezing spells had been recurring since February, 1932, without any remission. They had been quite acute, coming on suddenly at any time of the day or in the early morning hours. They were associated with a nasal discharge of watery fluid, free from pus. An episode of sneezing might last for an hour; but between them she would be free from all discomfort.

It is important to note, in the past history, that she had occasionally required treatment of the sinuses. An operation had been performed for an acute ethmoid infection in 1925. In 1926 she had spent eighteen months in Saranac because of tuberculosis of the right lung. It is, also, of importance

to mention the fact that she had had a tuberculous fallopian tube removed in 1930.

Our original examination showed a patient somewhat undernourished with an inactive pulmonary tuberculosis of the apex of the right lung. The blood morphology was entirely negative, except for a mild secondary anemia. There was no eosinophilia. Sputum examination and urine analysis were negative. x-Rays of the lungs confirmed the presence of an old fibroid lesion of the right apex.

Complete study of the allergic factors revealed nothing, except a violent reaction to orris root. As the patient was a nurse, it was quite difficult for her to avoid orris root. Therefore, specific treatment was prescribed. The schedule of treatment was as follows:

### CHART 2 TREATMENT SCHEDULE: ORRIS ROOT

1. Injections of dilutions of orris root extract were given subcutaneously without interruption for one year.

2. Treatment was given every third day.

Dosage: *Dilution 1:1000*

March 10 to March 25.

0.1 to 0.9 cc.

(6 doses)

*Dilution 1:100*

0.1 to 0.9 cc.

March 25 to April 7.

(6 doses)

*Dilution 1:10*

0.1 to 0.9 cc.

April 7 to May 5.

(8 doses)

After May 3, 0.9 cc. of the 1:10 extract was given once each week until April, 1934.

I kept in touch with this patient during the year following my first examination. The allergic rhinitis was relieved, but quite suddenly, in April, 1934, she began to complain of persistent cough and a definite asthmatic tendency. The cough had been frequent for at least a month before the reexamination was made; and every night upon retiring, she had been disturbed by prolonged paroxysms of asthma.

Examination showed numerous râles of a wheezing type throughout both lungs. She had evidence of an asthmatic bronchitis with definite emphysema. The allergic tests were repeated but no additional information was obtained, except a persistent reaction to orris root.

At my second examination a small nodule, measuring about 2 cm. in diameter, could be found in the right lobe of the thyroid gland. It was quite hard, and pressure induced cough. The basal metabolism was normal. It was my impression that this nodule might be larger than the external examination

indicated. I suggested the removal of the gland to eliminate pressure on the trachea. However, my medical associates were rather against this procedure, as the nodule was thought to be inconsequential. But because of the persistence of the cough, loss of weight, and the increased asthmatic discomfort, the patient finally submitted to operation. The right lobe was removed by Dr. William Rienhoff and much to our amazement a large mass, the size of a hen's egg, was found in the lobe projecting back against the trachea. It was quite firm, and on section was found to contain a large quantity of caseous matter. Pathologic sections confirmed our impression formed at the operation that this was a tuberculous thyroid gland. Its removal immediately relieved the cough and the bronchitis, and the asthma attacks ceased.

There has been no recurrence of asthma, excepting occasional wheezing after any acute respiratory infection.

This case is presented as an example of a number of similar patients whose condition might be considered as purely allergic, when as a matter of fact an intercurrent disease may prove to be the sole explanation of the symptoms.

I have on record 5 asthmatic patients sent to us for diagnosis of possible allergic phenomena; in all the simple removal of large adenomatous nodules in the thyroid gland relieved the pressure on the trachea and recurrent laryngeal nerve and at the same time cleared up the asthmatic symptoms.

**Case II.**—The patient, H. W., aged sixty-six years, was referred to me in January, 1937, with a history of recurring attacks of asthma beginning three years before, at the age of sixty-three. The attacks began with definite bronchitis, severe paroxysms of cough, and shortness of breath, both without and with exertion. For a time, he carried on his occupation as an architect without great discomfort. For the last year, however, he had been orthopneic. The attack of coughing had been violent. There had been continuous wheezing and difficulty in both expiration and inspiration. He had raised a rather thick, often foamy sputum, but free from blood. Occasionally, he had been able to control his asthmatic attacks with doses of adrenalin, but on admission to the hospital he had reached the point where any form of medication failed to relieve him.

When the patient was brought to Baltimore, he was in a semiconscious state due to the partial asphyxiation with which he was suffering. He was intensely cyanotic, his breathing was extremely labored, and there seemed to be greater difficulty with inspiration than with expiration. All accessory muscles were brought into play by his breathing. There was marked retraction of all interspaces with each inspiration, particularly on the right side. The veins stood out prominently on the neck throughout expiration as well as inspiration.

Examination showed four remaining snags in the lower jaw. The other teeth had been replaced by plates. There was rather marked emphysema, the costal angle measuring about 160 degrees. The diaphragm was low and excur-

sion was quite limited. Percussion of the lungs was everywhere hyperresonant. The breath sounds were distant, expiration being quite prolonged, and there were numerous sibilant scattered râles over both lungs. The heart showed a slight enlargement to the left and also to the right. There was a definite gallop quality to the sounds. The rate was 110. A soft systolic blow was heard along the left of the sternum. The first sound was reduplicated. There were no diastolic murmurs. The blood pressure was 110/84. There was moderate arteriosclerosis. He was undernourished for his age and height. His temperature was 100° F.

*Special Examinations.*—*x*-Rays of the sinuses were essentially negative. *x*-Rays of the teeth showed abscesses at the four roots. The electrocardiogram showed a normal sinus rhythm. The T waves were all upright. The first lead was normal. There was a sinus tachycardia. The PR interval was 0.16 second. There was, also, considerable depression of the ST interval both in the second and third leads; and it was our impression that the record contributed unquestionable evidence of some disease of the myocardium. The nose and throat examination showed an old infection of the antra and ethmoids, particularly on the right, but no surgical treatment seemed to be advisable.

The most important find in the routine laboratory examinations was the positive Wassermann. Antiluetic treatment was started, and within a week the elevation in temperature, which was found on admission, changed to normal. His cough gradually subsided. The asthmatic tendency diminished, and within eight weeks the patient was entirely free from the attacks. His general physical well-being was remarkably improved and he was discharged from the hospital, to continue his treatment elsewhere. The respiratory distress had all disappeared. The heart was still slightly enlarged, but the quality and rate of the sounds were normal.

I have delayed mentioning the *x*-ray of the chest until completing the presentation of this case. The *x*-ray study revealed an irregular shadow in the posterior mediastinum extending into each lung field, but especially marked on the right. The shadow was interpreted as a large mass of mediastinal glands. The lungs appeared to be clear.

On discharge from the hospital, the patient showed a striking improvement in the *x*-ray findings. The mass of glands had diminished in size, although they were still present. Fluoroscopy of the chest showed no evidence of respiratory embarrassment.

The patient returned for a check of his condition four months after the original study. At this time it was found that the glandular mass had completely disappeared and he was in splendid physical condition. Of course, the antiluetic treatment was being continued, the Wassermann still being positive.

In this case, innumerable protein tests certainly were not indicated. There was no definite basis for a diagnosis of allergic asthma, although this was the assumed diagnosis when he was brought to Baltimore.

These patients, therefore, emphasize the need for careful

consideration of all factors in differential diagnosis before it is assumed that allergy can explain the group of symptoms such as have been presented. In the first instance, the allergic rhinitis was a complication suggesting that the asthmatic attacks were just an added, more severe manifestation of the allergy. The second case, while unusual, should not be confused with any allergic phenomena.

### GROUP III

We shall now discuss a third group which will perhaps exemplify errors that the internist is liable to make if he is not familiar with allergic manifestations. Unfortunately instruction in allergy in our medical schools is still inadequate, probably because of the press of more important subjects, but not a little because the therapeutic results are appreciated only by the trained allergist.

The 2 patients now presented to you afford examples of true allergic hypersensitivity of a most striking type. These children had suffered with their manifestations since infancy. They were the same age and the etiologic factor was one that is frequently encountered and often overlooked by the internist in deciding upon his diagnosis.

Case I.—M. W., aged nine years, gave a history of having had attacks of asthma since the age of one and one-half years. The attacks were perennial in occurrence and were preceded always by coryza and slight soreness of the throat. There was no history of eczema or urticaria. The family history is important from the fact that the father had had eczema. For the three months before she came to us she had been confined to bed with continuous asthma of severe type. She had not been exposed to any unusual amount of powder nor to any domestic pets. Her physician had been unable to relieve her by the usual medication; adrenalin gave only transient relief. For the last three days her attacks had been so severe that she gradually had become cyanotic to such a degree that her physician felt that she might die at the height of an attack of asthma.

When the child was admitted to the hospital she was in a state of acute cardiac decompensation. The condition of the heart improved rapidly, however, under digitalis and much to my surprise two days after her admission to the hospital the asthmatic attacks ceased. Throughout the month's stay in the hospital she was entirely free from them.

The examinations, except for the condition of the heart, were entirely negative. She had an eosinophilia of 8 per cent. x-Rays of the chest and sinuses, eye examination, nose and throat examination revealed no abnormality. The protein tests by the passive transfer technic showed a marked sensitivity



to a number of inhalants, particularly to cotton seed. It was ascertained when the patient came to the hospital that for her entire life she had been sleeping on a cotton mattress. For three months previous to her admission she had been constantly lying on this mattress. Her dramatic improvement was the result of nothing more than the transfer from a cotton to a hair mattress.

Because of the difficulty in entirely avoiding cotton dust, it was thought advisable to give the patient specific treatment with a mixture of cotton seed and house dust. Treatment was started after she was discharged from the hospital and it has been continued up to the present time (two years).

When she entered the hospital the child was extremely undernourished, weighing only 60 pounds. Within a year her weight increased to 89 pounds, and she remained free from all respiratory symptoms. Our scheme of cotton seed dust desensitization has been as follows:

## CHART 3

## TREATMENT SCHEDULE: COTTON SEED LINT

Treatment was given every three to four days.

Dosage: 1:100,000

0.1 to 0.9 cc.  
(6 doses)

June 22 to July 6, 1935.

1:10,000

0.1 to 0.9 cc.  
(6 doses)

July 6 to July 27.

1:1000

0.05 to 0.9 cc.  
(10 doses)

July 27 to Sept. 21.

1:100

0.05 to 0.9 cc.  
(10 doses)

Sept. 21 to Nov. 12 when a constitutional reaction occurred, calling for reduction in dosage.

1:100

0.6 cc. 1:100 extract given every week and not increased, because repeatedly at 0.8 cc. the patient had violent constitutional reactions.

Nov. 12, 1935 to Sept. 1, 1936.

Note: Dilutions were made from concentrated cotton seed extract standardized at 0.7 mg. N per cubic centimeter.

Case II.—H. C. was first seen when he was two years of age in the children's clinic of the Johns Hopkins Hospital in 1926, because of recurring attacks of bronchitis. At that time no special studies were made to determine

whether he was allergic and he was not seen again until May 2, 1934, at the age of nine years. His mother said that since one year of age he had had recurring attacks of bronchitis and asthma. The attacks for at least five years were extremely severe and were thought to be due to an infection in his sinuses. There had at no time been a seasonal variation in the occurrence of the attacks nor had they been related to food nor to environment. They occurred both during the day and night. Between the attacks he had always had what were described as head colds. In 1932 in order to relieve these colds the tonsils were removed, but without any improvement. He had always been exposed to cats and dogs. He had seen a number of physicians before coming to the Johns Hopkins Hospital asthma clinic, and every effort to relieve infection had been made.

Physical examination revealed no serious abnormality. The nose and throat examination suggested an infection of both antra, and x-rays revealed a clouding of these sinuses. It was thought inadvisable to treat them radically because of his age. x-Ray of his lungs showed a moderate accentuation of root shadows. There were no enlarged glands. The heart was quite normal. The protein tests revealed sensitivity of a moderate degree to inhalants, but particularly to kapok. His sensitivity to cotton seed, however, was violent. Less than 0.05 cc. of a cotton seed extract containing 0.007 mg. of nitrogen per cubic centimeter produced a violent constitutional reaction. This reaction was so severe that for a period of two hours constant attention was required to combat the various allergic manifestations that presented themselves. In the sequence of events there was first an immediate laryngeal edema and generalized edema of the mucous membranes of the nose, throat and bronchi. There was violent asthma. To relieve him from these symptoms, it required 3 cc. of adrenalin solution (1:1000), given in divided doses over a period of one hour. After the asthmatic tendency had been controlled and the edema of the throat had subsided the patient developed generalized urticaria. This required an additional cubic centimeter of adrenalin solution (1:1000) in divided doses. The child remained in the hospital for twenty-four hours and seemed very much improved when he was discharged the following day.

An immediate clue was obtained from this violent reaction. The social service investigated the child's home. It was found that he was sleeping on a mattress stuffed with old cotton; much of the cotton was nothing more than floor sweepings or discarded ravelings from a cotton mill. There was a large tear in the mattress and, except for a thin sheet, the ravelings were in close contact with the child's face. Immediately a hair mattress was substituted and for a period of three years this child has reported to the clinic, when requested to do so, with a history of complete relief of the symptoms from which he had suffered since the age of one year. The congestion which had been present in the sinuses has cleared up and there is no evidence at this time of any sinus infection.

It is hardly necessary to call your attention to the fact that inexperience with the problems of allergy was responsible for the years of suffering of these children; in the one instance a fatality was just avoided.

## SUMMARY

These 3 groups are examples of errors in diagnosis made by the allergist on the one hand and the internist on the other. One must admit that a limited specialty is essential in the practice of medicine, whether it be cardiology, gastro-enterology or allergy, but the specialist must not become so warped in his knowledge that his earlier training is completely forgotten. The diagnostician likewise must not limit his knowledge to his basic foundation but should keep abreast of progress in diagnosis and therapy in the specific fields of medical science.

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**SYMPOSIUM ON ARTHRITIS**

The following clinics are included in this Symposium:

- R. Garfield Snyder: THE ARTHRITIS PROBLEM.  
Philip D. Wilson: SURGICAL RECONSTRUCTION OF THE ARTHRITIC CRIPPLE.  
Solomon Fineman: THE RÔLE OF THE ROENTGENOLOGIST IN THE DIAGNOSIS AND TREATMENT OF CHRONIC ARTERITIS.  
Martin Henry Dawson: THE RÔLE OF THE STREPTOCOCCUS IN CHRONIC ARTHRITIS.  
Clarence A. Dunn: ORAL FOCI IN ARTHRITIS.  
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## CLINIC OF DR. R. GARFIELD SNYDER

### HOSPITAL FOR THE RUPTURED AND CRIPPLED

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#### THE ARTHRITIS PROBLEM

1. A brief sketch explaining the reasons for the renewed interest in arthritis.
2. The American viewpoint on classification.
3. A discussion of the classification and treatment of arthritis of unknown etiology.

ARTHRITIS is a disease that has existed since the time of prehistoric man. In spite of the fact that it is probably more common than tuberculosis, heart disease, or cancer, it received but scant attention from the medical profession until comparatively recently. This lack of interest can be explained by the fact that arthritis is not a contagious disease, and is seldom fatal. Seventy per cent of the cases are chronic in character, and usually so insidious in onset that even the patient is loath to take his symptoms seriously. Inaccurate classification, lack of exact knowledge of etiology, and the poor results of treatment have long been discouraging factors in all efforts to conquer this disease.

The first serious organized efforts to study arthritis were instigated by some of the leading European governments because of the enormous and continued expense of treating this group of patients among the war veterans. In this country renewed interest in this problem was due largely to pressure exerted by the insurance companies whose main interest lay in shortening the period of disability of the sufferers from this disease.

The pioneer work of stimulating renewed interest on the part of the medical profession in the subject of chronic arthritis in this country was done by Dr. Ralph Pemberton and

Dr. Robert B. Osgood, who did the major work of launching the American Society for the Study and Control of Rheumatism and Arthritis. For the past four years annual meetings have been held in conjunction with those of the American Medical Association. These meetings serve as a center where all available information on arthritis can be discussed and critically evaluated. As a result, the subject has been considerably clarified and to some degree simplified. Although much progress has been made, there are still considerable differences of opinion on the classification, etiology and treatment of chronic arthritis.

For the past three years, the American and English literature on arthritis has been reviewed annually by the reviewing committee of the society. This has entailed an enormous amount of work on the part of the members of the committee. For the year 1935 alone over 600 publications had to be reviewed. Dr. Philip S. Hench and his committee deserve much credit for their untiring efforts to make these reviews comprehensive as well as justly critical. Anyone interested in the subject of arthritis can now be thoroughly informed on the important American and English literature by reading these excellent abstracts as they appear annually in the *Annals of Internal Medicine*. For the year 1936 the review will cover French and German literature as well.

It is now generally recognized that chronic arthritis is perhaps the most important economic problem that chronic disease presents. The previous, almost universal lack of attention to it was due partly to the confusing and discouraging differences of opinion regarding almost every phase of diagnosis and treatment of this malady. It has now been amply demonstrated, however, that in well-organized clinics a large proportion of chronic arthritis cases can be benefited by efficient and systematic treatment. In general from 50 to 75 per cent of the patients can be helped in some degree by proper treatment.

#### CLASSIFICATION

Up to now the complexity of the subject has made it seemingly impossible to arrive at a universally accepted classification of chronic arthritis. This is regrettable because it makes difficult the accurate comparison of the results of treatment

achieved in the various clinics of this country with the results obtained in the European clinics.

The following classification was compiled by the reviewing committee of the American Committee for the Control of Rheumatism and will be utilized to a large extent in the present discussion of this subject:

1. Diseases of joints related to trauma.
2. Diseases of joints due to infection of known type:
  - (a) Gonorrheal arthritis.
  - (b) Tuberculous arthritis.
  - (c) "Tuberculous rheumatism."
  - (d) Pneumococcal arthritis.
  - (e) Scarletinal arthritis; postscarlatinal rheumatism.
  - (f) Syphilitic diseases of joints.
  - (g) Undulant fever.
  - (h) Haverhill fever; erythema arthriticum epidemicum.
  - (i) Septic (purulent) arthritis.
  - (j) Arthritis of subacute bacterial endocarditis.
  - (k) Meningococcic arthritis.
3. Rheumatic fever.
4. Chronic arthritis of unknown etiology:
  - (a) Atrophic arthritis (rheumatoid, proliferative or infectious).
  - (b) Hypertrophic arthritis (osteo, degenerative or senescent).
  - (c) Backache and sciatica.
  - (d) Spondylitis:
    1. Atrophic and hypertrophic types.
    2. The "facet syndrome."
5. Gout and gouty arthritis.
6. Hemophilic arthritis.
7. Psoriatic arthritis.
8. "Allergic," "metabolic," and "endocrine arthritis."
9. Disease of muscles and fibrous tissues.

This classification is the one agreed upon by the reviewing committee; it does not necessarily represent the personal views of all members of the committee or of all the members of the American Society for the Study and Control of Rheumatism and Arthritis. This classification is admittedly not entirely satisfactory to all, but it is the best that has been devised to date.

The confusion in regard to classification is generally in relation to classifying accurately atrophic and hypertrophic arthritis, which, plus the mixture of the two types, comprise about 75 per cent of the cases that the general practitioner is

most likely to be called upon to treat. Because of its practical importance, it is with the group of arthritis of unknown etiology that this paper will primarily concern itself.

Atrophic and hypertrophic forms of chronic arthritis are diseases of unknown etiology. The synonyms most commonly used are rheumatoid for the atrophic form, and osteo-arthritis for the hypertrophic form. The writer prefers these terms for reasons which will be stated later in the paper. In rheumatoid arthritis, which occurs mainly between the ages of ten and thirty years, low-grade infection is presumed to be an important etiologic factor. In osteo-arthritis, occurring predominantly between fifty and eighty years of age, senescent degenerative changes of the joint structures, plus trauma and metabolic disturbances, are said to be important causative agents. While many cases fall into these two groups, it is our experience that the majority of cases do not lend themselves to such clear-cut distinction clinically, and for this group there is the necessity of an intermediate classification. In this paper they will be referred to simply as the mixed type of arthritis.

#### RHEUMATOID ARTHRITIS

**Etiology.**—Eighty per cent of the cases of rheumatoid arthritis occur between the ages of ten and thirty. The patients are usually underweight, flat-chested, and moderately anemic. Foci of infection, active or silent, can frequently be found. Trauma and metabolic disturbances are not important factors in this age group.

The term "rheumatoid" is appropriate because the specific causative organism is not known. The streptococcus is considered to be an important secondary cause. It cannot be regarded as the primary etiologic factor since no one as yet has succeeded in recovering it from the blood stream in a larger proportion of cases than can be found in control groups. Cecil, Nicholls and Stainsby<sup>1</sup> formerly thought that they could recover positive cultures from the blood and joint fluids in more than 60 per cent of their cases, but other workers have not been able to duplicate these results. Davidson and Goldie<sup>2</sup> state: "Our experience in cultivating blood and joint fluids both by the usual methods and by the special technique of the New York workers has been consistently negative."

Agglutination, precipitation, antistreptolysins and sedimentation tests have been utilized recently to emphasize indirect evidence in favor of the streptococcus as a primary etiologic factor. These findings are *indirect* evidence that infection, probably by the streptococcus, is present in the individual: they do not prove that the streptococcus causes the arthritis. Freeman, writing in the Second Annual Report of the British Committee on Chronic Rheumatic Diseases, points out that streptococci are just as adaptable in their immunologic reactions as in their growth characteristics.

Dienes and Bauer,<sup>3</sup> in evaluating these tests, found that the agglutination reaction is of definite aid in investigating the disease but is not practical as a routine test because of the difficulty of technic and the lack of uniformity in the findings. In their opinion the sedimentation rate is the most useful laboratory test for diagnosing cases of rheumatoid arthritis. It was positive in 90 per cent of their patients of that group. However, it was also positive in 50 per cent of the tests in 7 patients with osteo-arthritis and in both of their 2 cases of gout. In the writer's experience, the sedimentation rate was found to be an unreliable diagnostic and prognostic aid. We still employ this test as a routine procedure but find that it often does not agree with the clinical diagnosis or prognosis of the case. We agree with Hench<sup>4</sup> who stresses the fact that, since indirect tests are not yet of practical or of undoubted usefulness, we must continue to rely upon clinical judgment and observation in the management of chronic arthritis.

It seems to the writer that in the future studies of rheumatoid arthritis as well as of osteo-arthritis, our present knowledge will have to be supplemented not only by more specific information regarding the rôle of streptococci in these diseases, but also by a better understanding of the rôle of metabolic factors such as auto-intoxication, disturbances of liver function, and glandular secretion.

**Symptomatology.**—The onset of acute rheumatoid arthritis is very much like that of acute rheumatism. It is often marked by fever and prostration, but differs from rheumatic fever in that it seldom affects the heart and almost invariably causes some permanent damage to the joints. There is multiple joint involvement with pain, swelling and tenderness, and often

effusion into the joints. Chronic rheumatoid arthritis usually has a gradual onset and the inflammation in the joints is less pronounced.

### MIXED TYPE OF ARTHRITIS

In the second age group occurring predominantly between the ages of thirty and fifty, infection is still a prominent factor, but metabolic disturbances, mental and physical strain, and acute or repeated trauma, are increasingly important. A satisfactory inclusive term is needed to describe this group of cases in which the arthritis is so often of the mixed type.

### OSTEO-ARTHRITIS

**Etiology.**—The patients in the third age group suffer chiefly from osteo-arthritis, approximately 75 per cent of osteo-arthritis being seen in this age group. However, even in this age group one sees occasionally a typical case of rheumatoid arthritis.

Some prefer the term "degenerative arthritis"; others, the term "hypertrophic arthritis." The former signifies the degenerative process which is found in these cases in the soft tissues and cartilaginous portions of the joint; the latter is indicative of the hypertrophic bony changes also found at the periphery of the bones. Neither term is entirely satisfactory because of lack of inclusiveness and because of the assumption that infection does not play a rôle in this type of arthritis. Undoubtedly degenerative changes as well as chronic trauma, endogenous or exogenous in character, are important in the development of this type of arthritis. The writer, however, as well as other clinicians, believes that metabolic disturbances and low-grade inflammatory processes may bear a definite causative relationship to this disease. The possibility and the importance of infection in these cases decreases with the advancing age of the patient. Diminished capillary circulation around the joints is thought by some to be of etiologic importance in osteo-arthritis. While this may be true, Nissen<sup>7</sup> has pointed out that roentgen evidence of sclerosed blood vessels is found more often in rheumatoid than in normal controls of that age group. The factor of excessive weight per se, *i. e.*, as a trauma contributing factor, is also probably of minor



importance. These patients are not very much overweight, seldom in excess of 20 pounds.

**Symptomatology.**—Osteo-arthritis is seen ordinarily in fairly robust individuals past middle life. The chief complaints are stiffness and pain in the weight-bearing joints. Ankylosis and deformity are comparatively rare. The onset of the process is gradual and insidious.

It is argued by many that the only effective treatment in these cases is to put the painful joints at rest, to reduce weight, to attempt to increase joint circulation by physiotherapeutic measures, and to tell the patient that there is very little danger of joint ankylosis. We do not wish to belittle these forms of therapy. It is believed, however, that there is at present too great a tendency among clinicians to rely solely on such therapy to the exclusion of an endeavor to regulate the patient's metabolic processes and eliminate factors such as defective liver function, gastro-intestinal auto-intoxication or infection, and other low-grade infections of obscure origin. In our experience the possibility of obtaining a reasonably fair result in osteo-arthritis, if all these methods of treatment are kept in mind and utilized as indicated, is equal to the expectation of a good result in the treatment of rheumatoid arthritis. In spite of adverse criticism, we have insisted for years upon the primary importance of treating metabolic and low-grade infections in addition to the necessity of regulated rest and diet, and the elimination of trauma and postural strain. In 74 cases with osteo-arthritis that have been followed from three to fourteen years, treatment as advocated has produced an excellent result in 31 cases, fair in 15, slightly improved in 10, and has failed in only 18.

#### TUBERCULOUS RHEUMATIC ARTHRITIS

In Europe, particularly in France, a form of arthritis has been recognized in recent years called "tuberculous rheumatic arthritis." It was first described by Poucet in 1897 as a condition somewhat resembling acute rheumatic fever with pyrexia, pain and swelling of the joints, eventually terminating in a tuberculous arthritis of a single joint. Others broadened this concept and advanced the observation that in some cases it resembles atrophic. in others hypertrophic arthritis. The

opinion of the majority is that it represents an atypical tuberculous lesion since tubercle bacilli are not present in the joints. It is looked upon as an allergic manifestation in the joint due to tuberculous toxins from a distant tuberculous focus. In France, 12 out of 16 specialists in arthritis interviewed by Slocumb<sup>6</sup> considered this entity established. In this country, however, very few clinicians recognize this form of arthritis.

#### TREATMENT OF CHRONIC ARTHRITIS

**General Considerations.**—Interest in the treatment of arthritis was intensified in this country by Goldthwait and Billings some thirty years ago. Goldthwait emphasized postural defects and the value of controlled rest and exercise; Billings was the first to point out the necessity of the removal of foci of infection. A few years later Pemberton<sup>7</sup> showed that many of these patients were suffering apparently from a decreased carbohydrate tolerance, and were clinically benefited by reduction of carbohydrate intake. Billings's work stimulated bacteriologists in efforts to find a specific type of streptococcus as the etiologic factor in the disease. The belief became general and is still held by some that vaccines from specific isolated organisms would be as efficient in the treatment of arthritis as, for instance, the diphtheria toxin has been in the treatment of diphtheria.

A few years after Billings's original statement, Miller and Lusk<sup>8</sup> startled the medical profession by reporting a large series of arthritis cases that had been improved by treatment with nonspecific vaccines. Other workers<sup>9</sup> pointed out that the effect of these vaccines was due probably to the foreign proteins contained in the vaccines, and began to utilize other foreign proteins, such as milk and secondary proteins, with equally good results.

After the World War, the value of many forms of physiotherapy such as diathermy, ultraviolet light, baking, massage, and of hydrotherapy was investigated. The cooperation of orthopedic surgeons in the mechanical and surgical correction of joint deformities was sought and utilized. During the past five years efforts have been made to correct vitamin deficiency, or sulfur deficiency, which might be contributing causes in arthritis.

At various times each of the foregoing concepts was stressed, often to the exclusion of all other theories. Very often there was failure to mention in the literature that in addition to the favored remedy other forms of treatment had also been used. Recently, however, it has become the practice to utilize a combined program of treatment, including every recognized form of therapy which may be of value in each individual case. If a patient's economic status permits or if all indicated services and tests are available, they should be utilized. Very often this is not possible and the physician must select those measures which are least expensive and time-consuming, and which at the same time will most likely relieve the patient's symptoms and conserve joint function. It should be obvious that an acute arthritis in a young person demands more energetic measures to safeguard joint function than does an arthritic process in which function has already been seriously damaged. Similarly a patient with low resistance should be given treatments milder in character than would be given to one in robust health.

In the rheumatoid group, in which infection is the outstanding etiologic factor, the most clearly indicated method of attack is the removal of all offending foci of infection as rapidly as the patient's condition permits, the most easily accessible foci being removed first. In the quest for possible foci, all devitalized or crowned teeth should be viewed with suspicion. Devitalized teeth should be x-rayed at least once a year. The tonsils should be inspected for congestion of the anterior pillars and an effort should be made in every instance to force concealed pus from the tonsillar crypts. This is best done by applying pressure with a tongue depressor against the base of the anterior pillar. A latent sinus infection can often be detected by noting whether the patient has a high-pitched, nasal voice, or gives a history of postnasal drip. In every case the antra and frontal sinuses should be transilluminated. If roentgen examination of the sinuses is not available, the patient should be referred routinely to a rhinologist for examination and opinion. Finally, the lungs, gallbladder, gastro-intestinal tract, genito-urinary tract, and skeletal systems should be examined for evidence of infection or toxemia. The patient should be examined for flat feet and faulty posture so that an

effort may be made to eliminate these as contributory factors in the case. With the clinical facts to be obtained by thorough methods of examination, it is usually possible to plan a satisfactory therapeutic régime and to obtain beneficial results in a large proportion of cases of rheumatoid arthritis.

It is important to build up the patient's general resistance by proper diet, adequate elimination and a sufficient amount of rest. Ultraviolet light or infra-red radiation or a combination of both will be found useful for their tonic effect. The acutely inflamed joints must be immobilized for from six to eight days until the active phase of the disease has subsided and then passive and active exercises should be gradually instituted.

While under treatment, analgesics such as sodium salicylate or aspirin are given in maximum doses to relieve pain. For the relief of pain in the acute stage, heat in any form may be utilized, depending upon the facilities at hand: hot wet dressings, hot pads, hot-water bottles, carbon lamps, hot mud packs, or hot poultices. In the chronic stage, baking followed by general massage is probably most efficacious although diathermy and ultrashort wave treatment are preferred by many physicians.

In osteo-arthritis there is rarely bony ankylosis. It is excellent therapy to reassure the patient on this point. Foci of infection are not so important etiologically and for this reason should be removed only when specifically indicated. Old age is not in itself a strict contraindication if it is thought that such removal of a focus may benefit the patient. The patient's weight, if excessive, should be restored to a normal level by a proper dietary régime and medication.

Some cases may show a mild degree of glandular dystrophy. Treatment necessarily depends upon the type of glandular dysfunction present.

It is usually wise to insist on carefully regulated periods of exercise and rest in order to raise the patient's general resistance to the optimum. It is important to increase the elimination of all nitrogenous waste products, particularly uric acid, and for this purpose we give cinchophen routinely. In office practice baking and massage are easily administered. In clinics cabinet baths followed by hydrotherapy are best

utilized. If the joint symptoms are not relieved by these methods, and if roentgen examination reveals that the disability is due in part to mechanical obstructions in the joint, operative removal of bony spurs and "joint mice" is advised. One should be careful, however, in advising operative procedures when the temperature, leukocyte count and sedimentation rates are unduly elevated.

Patients with a mixed type of arthritis are the most difficult to treat. Here one must consider both the removal of all foci of infection and the correction of metabolic disorders caused by errors in diet. Other conditions to be treated are improper bowel elimination, postural strain, trauma, and glandular disturbances.

### METHODS

In the management of chronic arthritis the writer utilizes a combined method of treatment which, as a rule, embraces the following:

- Relief of mental depression.
- Controlled rest and exercise.
- Removal of foci of infection.
- Modification of diet when indicated.
- Drug therapy: aspirin and cinchophen.
- Vaccine therapy.
- Colonic irrigations.
- Physiotherapy and surgery.

In refractory cases the following methods of treatment are also utilized as indicated:

- Gold therapy.
- Sulfur therapy.
- Bee venom.
- Roentgen therapy.
- Vitamin therapy.
- Intravenous bilirubin and bile salts.

**Relief of Mental Depression.**—Insofar as possible, mental strain or depression should be relieved. While it may not be possible to eliminate worries of domestic or financial character, there is one source of worry which should be attacked vigorously, and that is the patient's constant fear that he is

afflicted with an incurable and progressively disabling disease. The patient should be told that there is a 70 per cent chance of obtaining a successful clinical result if he will make an earnest and sustained effort to cooperate faithfully with his clinician. The patient should be warned not to expect any rapid and spectacular results but rather a slow and gradual improvement. Nissen<sup>10</sup> believes that the mental depression is probably part of a poor constitutional background. The writer disagrees with Nissen's viewpoint. He believes, however, that exhaustion of the nervous system contributes to lowering the patient's resistance and thus permits the other etiologic factors of arthritis to gain a foothold. His experience has been that the state of mental depression almost invariably disappears with the progressive improvement of the arthritis. Recently Cobb, Whiting and Bauer<sup>11</sup> reported that they had found mentally upsetting factors at work in a majority of arthritis patients for from six months to several years prior to the appearance of symptoms.

**Controlled Rest and Exercise.**—Adequate or complete bed rest is of primary importance in cases with acutely inflamed joints. After the initial inflammatory stage has passed, however, it is generally not necessary for the patient to remain in bed. The physician should insist, however, upon a rest period of an hour or two during the afternoon. Prolonged bed rest is contraindicated because of the danger of loss of motion from joint adhesions and from possible ankylosis. Exercise in bed *under medical supervision* should be started as early as possible in every case, and continued when the patient is out of bed. In this way the normal range of motion can very frequently be reestablished. The important point to remember is that the patient must have the proper amount of sleep. If exercise is not carried out to the point where it results in pain with loss of sleep one need not fear that exercise will prove harmful to the patient.

**Removal of Foci of Infection.**—It is difficult to understand the reason for the conservative attitude maintained by many clinicians in regard to the removal of foci of infection, as in many cases spectacular results are obtained following such removal, especially in young people. While the beneficial results obtained in older people are not so startling, neverthe-

less, in the majority of cases the results warrant the slight risk involved. While the results of removal of infectious foci are more brilliant in the rheumatoid type of arthritis, sufficient benefit to the patient is also obtained in the osteo-arthritic type to warrant this procedure as part of the combined attack of the clinician in fighting this disease.

(a) *Tonsils* as a rule are the most important source of infection and should always be removed in a patient with a history of repeated attacks of tonsillitis or if pus can be expressed on pressure against the base of the anterior pillar. In suspected cases of tonsillar infection it may be necessary to use suction in order to establish the diagnosis of latent infection. A frequent source of infection is to be found in the remnants of tonsils previously removed either by surgery or by electrocoagulation. Even if the presence of pus cannot be demonstrated in the tonsils at one or two examinations, persistent congestion of the anterior tonsillar pillars is presumptive evidence that a low-grade tonsillar infection is present.

(b) *Teeth* are next in importance as potential foci of infection. It is advisable to obtain a complete roentgen examination of the mouth in every patient. Devitalized, crowned and filled teeth should receive particular attention. All teeth showing apical abscesses should be removed in the early stage of treatment. The decision as to whether a dead tooth should be removed is sometimes difficult to make, and in general should be made after due consideration of the following: if the root canal of a single root tooth is completely filled, there is probably little danger of infection from this source; if incompletely filled, it should either be removed or the root should be properly filled. All devitalized teeth with multiple roots are to be regarded with suspicion, even though they do not show apical abscesses. It is very difficult, as a rule, to fill these root canals on account of their tortuosity. In patients whose teeth have been partially or wholly removed it is wise to examine the jaw roentgenographically to be sure that no infected root fragments are still present.

(c) *Sinuses*.—While acute sinusitis is usually associated with unmistakable pain over the affected sinus or by severe and uncontrollable headache, in many cases the onset is more insidious and the typical severe frontal or occipital headache

or pain over the antra may be absent.<sup>12</sup> In these cases a low-grade infection may exist in the sinuses and be entirely unsuspected by the patient and his physician. This is particularly true in the damp, quickly changeable climate such as is found on the Eastern coast. In rare instances these sinus infections may escape detection by the radiologist, but even these rare cases can be accurately diagnosed by the combined efforts of a competent radiologist and rhinologist.

If the sinus infection is of moderate severity, cases are sometimes handled successfully by the ultraviolet light, diathermy, or ultrashort-wave treatment. Others require one or more series of sinus irrigations to effect an improvement in the condition of the sinuses. In our experience irrigating methods have been relatively successful in the acute cases. In chronic sinusitis where definite chronic inflammatory change of the mucous membrane has taken place, it may be necessary to resort to radical surgery in order to clear up the focus of infection. In a carefully selected group of our cases this procedure has been carried out with very satisfactory and permanent results.<sup>12</sup> In both the acute and intractable cases it may be advisable to send the patient to a warm, dry climate such as in Arizona or New Mexico.

(d) *Remote Foci of Infection.*—Foci of infection occasionally occur in the lungs, gallbladder, gastro-intestinal and genito-urinary tracts and skeletal structures. These foci should be studied as possible etiologic factors. Due to inaccessibility, the risk entailed by their removal is correspondingly great, and it is our custom to defer the removal of such foci as long as possible, in the handling of an intractable case. The writer has not seen a single instance where the removal of a focus of infection permanently aggravated the arthritis. Many physicians object to the removal of such foci on the ground that they have not observed beneficial results following this procedure. It is possible that in such cases the foci of infection were incompletely removed or that other unsuspected foci were overlooked and continued to act as a source of infection. Our experience coincides with that of Pemberton<sup>13</sup> who found, in a careful review of 300 cases in which the focus of infection was supposed to have been entirely removed, that 79 per cent with atrophic and 81 per cent with hypertrophic arthritis still



harbored foci of infection when they came to him for examination. Removal of such unsuspected foci has often proved most helpful in obtaining a satisfactory therapeutic result.

**Diet.**—The earlier workers in the field of arthritis were firmly convinced that an excessive intake of proteins or purins was an important etiologic factor in the production of chronic arthritis. At that time, however, the clinical differentiation between chronic arthritis and gout was not sharply defined. Pemberton first pointed out the etiologic importance of an excessive carbohydrate intake, and as a result a great majority of the cases of chronic arthritis were placed on rigidly restricted diets, sometimes to the detriment of the patient.

Gradually it became apparent that in chronic arthritis we are dealing with two types of individuals: one, the undernourished individual, found mainly in the younger, infectious or rheumatoid group, and the other, the moderately overweight individual, found mainly in the senescent or osteo-arthritic group. In the former, it seemed unwise, due to already lowered resistance, to deplete vitality any further, and physicians began to advise placing these patients on a full diet with adequate vitamins to build them up. Fletcher<sup>14</sup> advanced the theory that a diet low in vitamin B was an important factor in the production of chronic arthritis because this deficiency leads to colonic dilatation, intestinal stasis and poor elimination. The accuracy of this view will be discussed later in connection with other forms of vitamin therapy.

Many patients who are overweight are undoubtedly benefited by restriction in diet, to the point where their weight becomes normal. The rationale for the improvement in these cases is still under discussion. Pemberton feels that a reduced carbohydrate intake produces a reduction of the metabolic load which in some manner, as yet not clearly understood, benefits the joints. With this view the writer is in complete accord. Others believe that carbohydrate restriction in arthritis has no beneficial effect except that it reduces the weight of the patient and so lessens the load on the weight-bearing joints. This argument seems weak because one sees a great number of people in America who are moderately overweight, but only a relatively small proportion of overweight individuals suffer from arthritis.

Langstroth<sup>15</sup> advanced the theory that rheumatoid arthritis may be due to diets that are relatively low in protective foods such as fresh fruits, and are also low in calories. Boots<sup>16</sup> believes that a low carbohydrate, low protein diet does more harm than good. Pemberton considers the edema of arthritis to be due to a low serum albumin, and for this reason regards protein restriction as harmful. Lockie<sup>17</sup> found that restriction of carbohydrates is of no particular merit and that an excessive intake does no apparent harm. Hench<sup>18</sup> reported that the administration of 400 to 800 Gm. of carbohydrates daily for many weeks did not bring about a recurrence of symptoms in cases of atrophic arthritis where symptoms had been temporarily inactivated by the presence of intercurrent jaundice.

There is no general agreement on the subject of diet. It has been our practice to regulate diet according to what appear to be the requirements of the patient, taking into account his appearance, weight, blood chemistry values, and the probable efficiency of elimination.<sup>19</sup> The basic diet should, as a rule, be as generous as possible and include as much fresh fruit, raw vegetables and milk as is consistent with well-being and the maintenance of normal blood chemistry values. We usually restrict the carbohydrate intake if the blood sugar is above 120 mg. per 100 cc. of blood. We also restrict the intake of proteins and purins if the blood uric acid is above 3.5 mg. per 100 cc. Fats are restricted if there is a history of cholecystitis.

**Drug Therapy.**—The writer depends largely on the use of cinchophen and aspirin in the routine treatment of chronic arthritis, beginning with 7.5 grains cinchophen three or four times a day. If this is not sufficient to control the pain, an additional 5 grains of aspirin four times daily is advised. Cinchophen is never increased beyond this limit because of the possible danger of cinchophen poisoning.<sup>20</sup> Apparently this is a safe dose because for the past fourteen years we have used cinchophen in this manner in the arthritic clinic in the Hospital for Ruptured and Crippled, as well as in private practice, without any serious toxic effects. During the first two weeks of treatment the patient should be seen at least three times a week, and later not less than once a week, as long as cinchophen is being administered. Signs of skin irritation, particularly itching, are looked for. If such irritation occurs, all medica-

tion is immediately stopped until the skin irritation disappears. We have occasionally encountered a slight degree of urticaria which has persisted for one or two days and occasionally as long as a week. Itching and urticaria can usually be promptly controlled by hypodermic injections of 10 minims of adrenalin, repeated every two or three hours if necessary.

Cinchophen is a very important drug for which there is no substitute. It is the only one that controls pain and has a definite chologogic effect. The combination of aspirin and cinchophen in the dosages mentioned seems to be sufficient to control the pain in the great majority of all cases of chronic arthritis. It is unnecessary to use narcotics except in occasional instances. If the pain is not entirely controlled by the dosage prescribed, or if there is evidence of gastric irritation, we have found that we can obtain alleviation of pain by giving relatively large doses of sodium salicylate per rectum. In obstinate cases we not infrequently give as high as 200 to 300 grains of sodium salicylate in this manner. In the cases in which it is necessary to stop all medication because of transient urticaria, cinchophen medication can usually be resumed successfully after the urticaria subsides, by starting with very small doses, or by substituting tolysin for cinchophen.

Many authorities prefer neocinchophen or tolysin to cinchophen, as these are supposed to be less toxic. They are also definitely less efficacious and consequently larger doses of these drugs must be given to obtain satisfactory results.

**Vaccine Therapy.**—In spite of skepticism expressed by some members of the medical profession in regard to this method of treatment, vaccines have a definite therapeutic value in the treatment of chronic arthritis. They probably act by stimulating the reticulo-endothelial system and produce increased leukocytosis.

If large doses are given intramuscularly or smaller doses intravenously, the temperature usually rises from normal to 100° or 102° F., and by increasing the dosage it can be raised gradually up to 107° F.<sup>21</sup> It was originally thought that the increased temperature might be the chief cause of the beneficial effect, the increased heat probably inhibiting the growth or actually killing the bacteria in the blood stream. However, this possibility is a very remote one, because the only

organism that might be susceptible to this temperature would be the gonococcus. The streptococcus which is the organism generally believed to be associated with arthritis is even more resistant to heat, and most workers hesitate to subject their patients to the risk of temperatures higher than 106° F. The chill is another factor which may be responsible for the beneficial results observed following vaccine therapy. During a chill, there occurs a systemic dilatation of the capillaries and increased circulation may have some beneficial effect.

Although the exact explanation of the benefits derived from vaccine therapy to date is not entirely clear, there can be no question that beneficial results are occasionally observed. Conservative workers put the ratio of improvement at 1 in 4 cases, but even this ratio is worth remembering when treating the refractory case.

Originally there was great enthusiasm for autogenous vaccines. Gradually it became evident that stock vaccines produced equally good results. Miller and Lusk reported a large series of cases of acute, subacute, and chronic arthritis successfully treated by the use of typhoid vaccine. Following this report the writer in 1915 attempted to confirm these results, working on the problem during the following three years in the City Hospital of New York. He found that typhoid vaccine was of definite benefit in the treatment of many cases of acute arthritis but that in chronic arthritis the amount of benefit usually varied in inverse proportion to the length of time the patient had been suffering from the disease. Since 1918 the author has continued to use typhoid and streptococcus both in private practice and in the clinic. Unless the patient can be hospitalized it is better to administer the vaccine subcutaneously or intramuscularly.

Most workers now use either a stock streptococcus vaccine or a streptococcus vaccine prepared on the basis of skin sensitization tests or serum agglutination tests. Many use relatively large doses, others prefer to give the vaccine in small doses with the idea of desensitizing the patient rather than with the intention of precipitating "shock," that is, chill and high temperature. The writer has tried various methods during the past twenty years with the exception of vaccines prepared on the basis of skin sensitization tests. He is not convinced

yet of the practical value of autogenous vaccine therapy. It must be admitted, however, that opinion regarding the efficacy of vaccine therapy is purely a personal matter. It is almost impossible to compare the results obtained by different men because no two physicians ever treated the same series of cases and rarely even the same patient under similar circumstances. There is, however, no contraindication to the use of autogenous vaccines other than the seemingly unnecessary expense entailed in their preparation. Short, Dienes and Bauer<sup>22</sup> state that none of the various methods recommended for the selection of strains from which to make specific vaccines has a solid theoretical or experimental foundation.

As a rule, the object of administering vaccines by the intravenous method is to obtain beneficial results rather rapidly. Small doses, however, may be entirely ineffective and large doses may be dangerous or even fatal. The writer, therefore, usually employs medium doses intravenously.

The slower, safer method of intramuscular or subcutaneous injection is more desirable in office and clinic practice. For routine treatment we use stock nonhemolytic streptococcus vaccine beginning with 2 minims administered subcutaneously twice a week. The dose is increased gradually at each injection until a local or general reaction is obtained. The dose is then maintained at this level for two weeks, after which it is increased to the point where a second reaction is obtained. If the stock vaccine thus used does not seem to be beneficial, we may change to Coley's mixed toxins. It should be remembered, however, that while Coley's toxins are apparently somewhat more efficient than stock vaccines they are more apt to give undesirable urticarial reactions. These reactions occur suddenly, may continue for a week and be most annoying both to the patient and the physician. They are best controlled by ephedrine sulfate,  $\frac{3}{4}$  grain by mouth, three times a day.

The writer is unaware of any contraindications to vaccine therapy. For the patient whose resistance is unusually low it is always advisable to start with a very small dose and build up the dosage less rapidly than in the case of the robust patient.

**Colonic Irrigations.**—Colonic irrigations have proved very helpful in the management of individuals who clinically appear to be suffering from intestinal toxemia as indicated by

sallow skin, coated tongue, mental irritability, fatigue, nausea, flatulence, headaches, and constipation. The exact explanation of the good results is not clear, but the improvement would seem to be due largely to the removal of toxic products originating in the colon, rather than to the direct action of colonic irrigation solutions on the bacteria themselves. Hensch pointed out recently the relative rarity of articular disease in known infections of the colon such as severe ulcerative colitis with diarrhea, blood and pus in the stools. Actually, he points out, arthritis complicates bacillary dysentery in only 3 per cent, ulcerative colitis in only 4 per cent, and typhoid fever in 10 per cent of cases. This relative rarity of arthritis in patients with a specific infection of the colon, however, does not eliminate the possibility that toxic products originating in the colon, either from bacterial activity or from improper digestion, may be absorbed through the portal circulation and become a causative factor in chronic arthritis. It is possible, therefore, that the beneficial effects of colonic irrigations are due to the fact that a considerable quantity of the irrigating solution is absorbed through the portal system, thereby diluting toxins in the portal circulation and liver. Large numbers of bacteria as well as accumulation of toxic products are undoubtedly removed mechanically from the intestine by means of colonic irrigations, and we believe that when beneficial results do not follow colonic irrigations, it may be because the colonic irrigations in these cases were not given efficiently. It is not generally appreciated by the laity or by the medical profession that it requires an especially skilful technic on the part of the nurse properly to administer a colonic irrigation which will satisfactorily remove deleterious intestinal products. This type of therapy has unfortunately been exploited by laymen and has fallen into disrepute in some medical circles. In our own experience colonic irrigations have proved to be an invaluable adjunct in the management of chronic arthritis.<sup>21</sup>

**Physiotherapy and Surgery.**—These methods of treatment will not be considered in this article because of their detailed presentation by other contributors to this symposium.

## NEW METHODS OF TREATMENT

**Gold Therapy.**—Gold therapy has been used extensively in France and England for a decade. It is not surprising that the pioneer work in chrysotherapy has been done in France because the French believe that rheumatoid arthritis is very closely associated with tuberculosis. Forestier<sup>24</sup> conceived the idea that since gold therapy was beneficial in tuberculosis, it might also prove to be beneficial in chronic rheumatoid arthritis. He began his investigation in 1928, and recently reported a six-year study of a series of more than 500 cases, in 60 per cent of which satisfactory results were claimed. In his opinion gold therapy is our most valuable therapeutic agent in treating this condition. He is supported by several co-workers in France and by certain prominent English authorities. American workers, however, have pointed out that the percentage of successful results obtained by orthodox methods used here compare favorably with the results of gold therapy abroad. Moreover, it has been felt that our conservative methods are relatively safer because all gold salts are known to be definitely toxic.

In spite of the fact that Forestier's reports have not been received with great enthusiasm in America, we decided to test for ourselves the efficiency of this method. Appreciating, however, that it is a dangerous drug we proceeded to use it with caution.

We started experimenting with this method two years ago with an initial dose of 10 mg. of gold sodium thiosulfate given intravenously, gradually increasing the amount with each injection. The largest dose we have given in any case was 120 mg. A series of 8 injections at weekly intervals is given and then a rest period of one month is allowed. Following this, a second series of 8 injections is carried out. We insist upon a urine examination before each weekly injection for traces of albumin and urobilinogen. If either is present, treatment is discontinued until the albumin and urobilinogen have disappeared.

To date we have given more than 2000 injections of gold sodium thiosulfate intravenously, and have noted only 18 toxic reactions, the majority of which were in the form of a mild skin eruption which persisted for less than a week. However,

one patient developed a troublesome dermatitis that lasted for two months and another developed an edema of the glottis in which it became necessary on the fourth day to do a tracheotomy for relief of the dyspnea. In both instances the initial dose was 10 mg. and the second dose, given four days later, 20 mg., following which the reactions occurred. In each patient the symptoms completely disappeared. There have been no deaths.

In general the results of this form of therapy were satisfactory. Varying degrees of improvement were obtained in patients who were refractory to other forms of therapy. It may be concluded, therefore, that cases which do not respond to the usual forms of treatment, including vaccine therapy, should be given the benefit of a trial with gold salt therapy. Extreme care, however, must be used in administering this drug.

**Sulfur Therapy.**—Many authorities believe that sulfur deficiency is a prominent factor in the production of arthritis and that, to cure the disease, it is necessary to give sulfur in some easily available form. They support this contention by citing the fact that in some cases of arthritis the cystine content of the body as determined from the finger nails is frequently low, and claim that by giving a sufficient amount of sulfur intravenously or intramuscularly the cystine content can be elevated to normal with accompanying clinical improvement.

Rawls, Gruskin and Ressa<sup>25</sup> have reported that of 33 patients with atrophic arthritis treated in this manner 15 were improved; those with the lowest cystine content received the greatest benefit. Wheeldon<sup>26</sup> has reported 892 cases treated with 40 intravenous and 40 intramuscular injections of sulfur; every case was improved subjectively. Muscle spasm improved in 85 of the cases and joint pain was helped in 65 per cent. Woldenberg<sup>27</sup> treated 231 patients with excellent clinical results, the greatest improvement having been noted following the intravenous administration of 30 mg. sulfur daily for ten days. The majority of his patients were free from pain after 3 to 5 injections. He admits, however, that these patients were also given physiotherapy treatments daily.

The writer's experience with this method has been too limited to date for an expression of opinion as to its value. Following large doses intravenously, patients are apt to de-



velop fatigue, headache, anorexia, nausea, vomiting, chills, and fever; in other words, a typical foreign protein reaction. Sulfur dermatitis is not uncommon. This form of therapy needs further investigation.

**Bee Venom.**—This method of treatment has been used extensively from time to time in Europe and to a certain extent here. For centuries beekeepers have insisted that their occupation prevents the development of arthritis, and that if a patient with arthritis took up beekeeping his arthritis would almost invariably disappear. The literature is full of instances in which physicians have become interested in this form of therapy and have tried to determine its exact field of usefulness as well as to develop some practical method of giving the treatment. Bee venom therapy has certain decided disadvantages. In the first place, it is an impractical form of therapy to administer. Secondly, the efficiency of bee venom depends upon its virulence, and, unfortunately, virulence declines and almost entirely disappears during the cold winter months. We have been testing this form of treatment for the past six months at the clinic on arthritis at the Hospital for the Ruptured and Crippled. To date we have noted an undeniable improvement in several cases that had been very resistant to every other form of treatment.

There are many reports in the literature where an accidental bee sting has actually killed a person. Fortunately, however, patients with arthritis seem to be definitely immune to the poisonous effect of bee venom and many of them can eventually tolerate up to 30 or 40 bee stings at one treatment, without undue toxic effect.

The irritated part becomes inflamed and congested, and this congestion persists for many hours, even days. Usually treatment is commenced with the application of one bee sting and is increased as rapidly as the tolerance of the patient will permit. Patients are subjected to bee sting once or twice a week. The joint is first anesthetized by spraying ethyl chloride on the area to be stung by the bee.

An attempt has been made to prepare bee venom artificially and this is now available in the form of Apicosan. This would be an ideal method of administering bee venom but so far the results with it in our clinic have been unsatisfactory.

The rationale of the treatment is not yet understood. Its action may be similar to the action of vaccine or foreign protein. However, many workers believe that there is an intrinsic property in bee venom which makes it more efficient than either vaccine or other foreign protein therapy. There is another possibility; that the beneficial results may be due in part to the resultant increased capillary circulation.

**Roentgen Therapy.**—The writer feels that roentgen therapy deserves greater investigation than it has had so far. Although we have not had extensive experience with this method it has been definitely beneficial in several refractory cases. The experience of Garland<sup>28</sup> with 30 cases of gonococcal arthritis treated by roentgen therapy led him to conclude that it is equal if not superior to fever therapy and recent reports from England tend to bear out this statement.

**Vitamin Therapy.**—The ingestion of large amounts of vitamin B has been recommended by Fletcher who believes that the sluggish and atonic colon so often present in these cases is due to vitamin B deficiency. He claims that the ingestion of this vitamin improves the tone of the colon which in turn, by improved elimination, helps in the cure of the arthritis. Snyder and Fineman, in a discussion of Fletcher's paper at the conference of the Committee on Arthritis in Milwaukee, in 1933, stated that they could not substantiate Fletcher's results since they had been unable to duplicate his roentgen evidence of the colon changes. A general tonic effect was noted in the patient after excessive feeding of vitamin B, but no beneficial local effect in the arthritis.

The excessive ingestion of vitamin C has been advocated by Rinehart and his associates<sup>29</sup> because, by its deprivation, they were able to produce an arthropathy in guinea-pigs which they considered to be very similar to chronic arthritis in the human. It was shown that a superimposed infection usually accentuated the production of the arthritis. With adequate vitamin C nutrition, however, arthropathy could not be produced in the guinea-pig even when it was subjected to coincidental infection. Some of Rinehart's arthritic patients showed clinical evidence of vitamin C deficiency. In spite of these interesting findings, Faulkner<sup>30</sup> and Bauer concluded that vitamin C deficiency plays no rôle in chronic arthritis. Bauer's patients

who adhered to a high vitamin C diet for from three to five years were no more improved than patients not so treated. Although Rinehart believes that his animal experimental lesions closely resemble those of arthritis in the human, other workers have failed to note the close similarity and doubt the accuracy of his test for vitamin C deficiency.

Dreyer and Reed<sup>31</sup> reported in 1935 that they had placed 34 patients with atrophic arthritis on massive doses of vitamin D and that 25 were improved. They noted also some improvement in patients with hypertrophic arthritis. In a few instances this improvement was noticeable after a week; in other patients six months' treatment was required. The patients were given 200,000 U.S.P. or international units of vitamin D daily for one month. If relief was noted, the dose was reduced to 50,000 or 60,000 each week. Toxic symptoms, consisting of nausea, frequency of urination, diarrhea, vomiting and abdominal pain, occurred in a small percentage of cases. To combat this toxicity, the drug was discontinued. We are at present testing this form of treatment in a group of 30 patients. Most of these patients have shown a general tonic improvement during the past year, but the arthritis has thus far remained almost unchanged.

**Bilirubin and Bile Salts Intravenously.**—Recent reports by Hench<sup>32</sup> and Thompson and Wyatt<sup>33</sup> tend to indicate that the liver is an important organ in the problem of chronic arthritis. Hench describes 31 cases that were absolutely free of all arthritic symptoms during and for several weeks or months subsequent to the onset of an intercurrent jaundice. Thompson and Wyatt report that they were apparently able to cure intractable cases of chronic arthritis by an artificially induced jaundice, through intravenous administration of large doses of bilirubin and bile salts.

### CONCLUSIONS

1. Treatment to be successful must be adapted to the individual patient.
2. Beneficial results are rarely observed in arthritis in less than three months: many require from one to three years of persistent treatment. The physician must exercise sound judgment in deciding which foci of infection are to be removed and

the time and sequence of their removal. He must study carefully in each case the type and amount of medication to be given. Many failures in the treatment of arthritis can be attributed to insufficient attention to details and lack of vigorous attack. Such drugs as cinchophen, tolysin, aspirin, gold salts, and sulfur must be carefully controlled but given to the point of tolerance.

3. The physician must endeavor to overcome the mental depression of the average patient suffering from this disease. In spite of the fact that we are still in the dark as to the underlying cause of chronic arthritis and are unable for that reason to direct treatment against the specific etiologic factors, diligent application of our present knowledge will often result in a satisfactory or even at times spectacular improvement in the patient's condition.

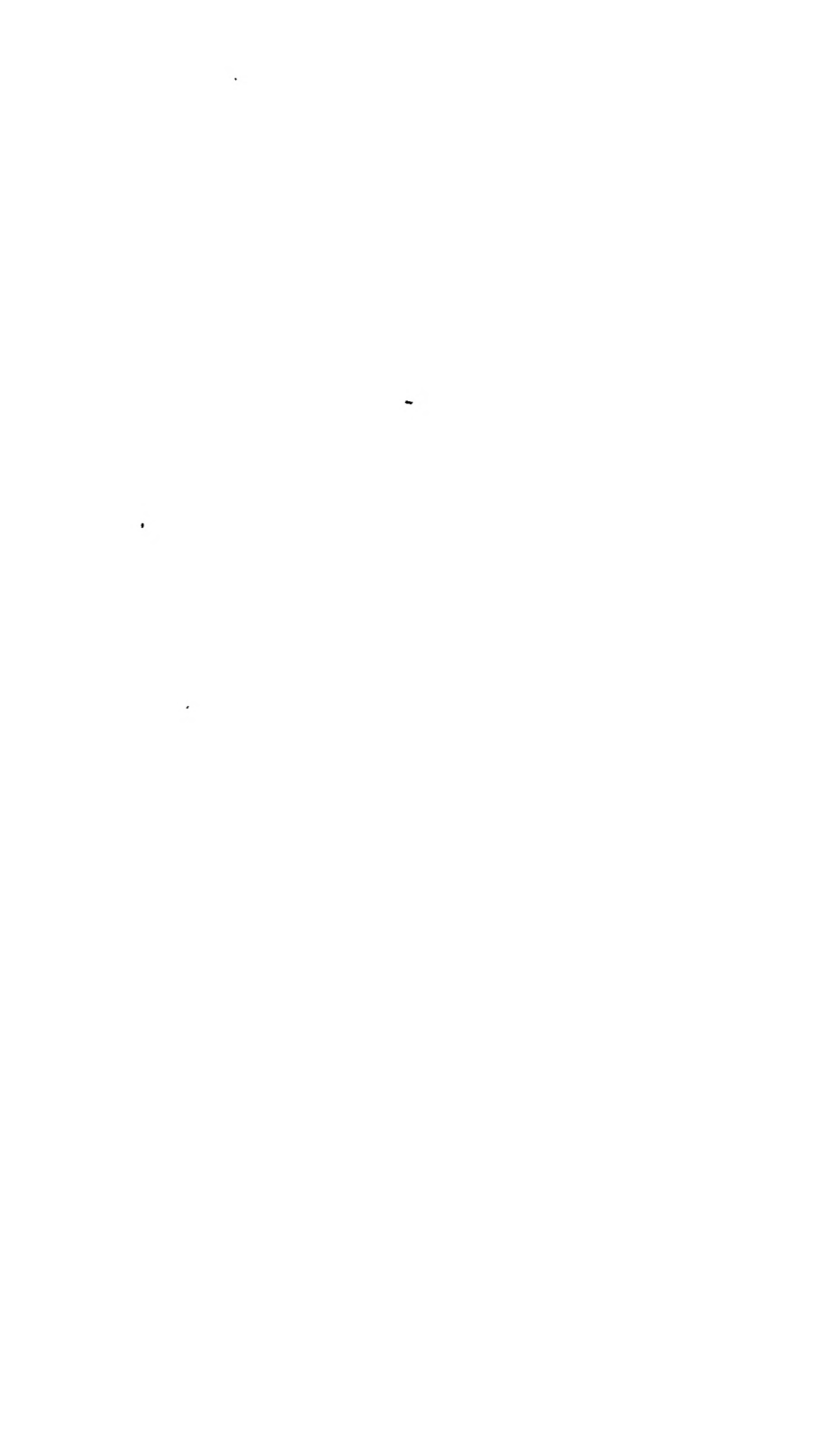
4. Inasmuch as there is as yet no absolute evidences that rheumatoid arthritis and osteo-arthritis are distinct entities of different etiology, the physician must bear in mind when treating osteo-arthritis as in rheumatoid arthritis, the possibility of the presence of foci of low-grade infection as well as of intestinal toxemia. He must also regulate metabolic and glandular disturbances in addition to carrying out the generally accepted methods of treatment of arthritis, such as reduction in weight, elimination of trauma, improvement of circulation and the institution of an adequate amount of rest.

5. In the entire field of medical practice there is no more grateful patient than the sufferer from arthritis who has been relieved of his symptoms and restored to economic usefulness.

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## CLINIC OF DR. PHILIP D. WILSON

### HOSPITAL FOR RUPTURED AND CRIPPLED

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#### SURGICAL RECONSTRUCTION OF THE ARTHRITIC CRIPPLE

WHILE the general and systematic treatment of chronic atrophic arthritis is largely a medical problem, certain aspects of the disease have always been and will continue to be of great interest to the orthopedic surgeon. These have to do chiefly with the prevention and correction of joint deformity during the active phase of the disease and with measures to obtain restoration of function in badly damaged joints when the disease has reached an inactive stage. It is the latter part of the therapeutic problem that I shall attempt to consider here. While it represents but one small phase of the large problem of what to do for the arthritic cripple, it is an important one in view of the many brilliant results that have been obtained in the past and also one that is poorly understood and frequently neglected by the medical practitioners who stand in closest relation to the patients.

May I make clear at this point that between the two great types of arthritis, the atrophic and hypertrophic, I shall confine my discussion entirely to the former. While hypertrophic arthritis presents its own special questions and is frequently amenable to surgical treatment, there is no doubt that atrophic arthritis represents the greater part and the more complicated part of the therapeutic problem and we shall have enough to occupy us if we consider it alone. Let me remind you that in atrophic arthritis, otherwise known as rheumatoid, proliferative or infectious arthritis, the characteristic pathologic changes are of a proliferative nature, first affecting the synovial membrane with secondary invasion of the articular cartilage. The process is definitely ankylosing in tendency and for this reason

prolonged immobilization is dangerous and should always be avoided.

In atrophic arthritis we have to deal with a general disease and health problem in addition to the local problem of relieving a cause of disability. Fortunately there are encouraging features of the disease which should be recalled along with the discouraging one. Every physician who has had much experience with arthritis has seen patients in whom, for one



Fig. 110.—Case 1. Chronic synovitis of left knee A, Preoperative B, After synovectomy.

reason or another, the disease has been arrested and who have remained in good health for years. Such patients may be terribly crippled, confined to bed or to wheel chairs, and unable even to feed themselves, but the essential point is that their condition has remained stationary for many years or, in other words, that the arthritic fires have been extinguished and that their disabilities are due to joint damage which the healing processes of the body have been unable to repair. In this connection it must always be remembered that abundant experimental evidence exists to show the limited healing powers of



joints in general and of articular cartilage in particular, especially in adults.

**Surgical Obstacles.**—No problem is more appealing than that of the rehabilitation of arthritic cripples, but unfortunately the surgical attack upon the disabled extremities is attended by many difficulties and their solution calls for the soundest judgment and highest skill. The chief difficulty is constituted by the fact that usually there is multiple joint involvement and

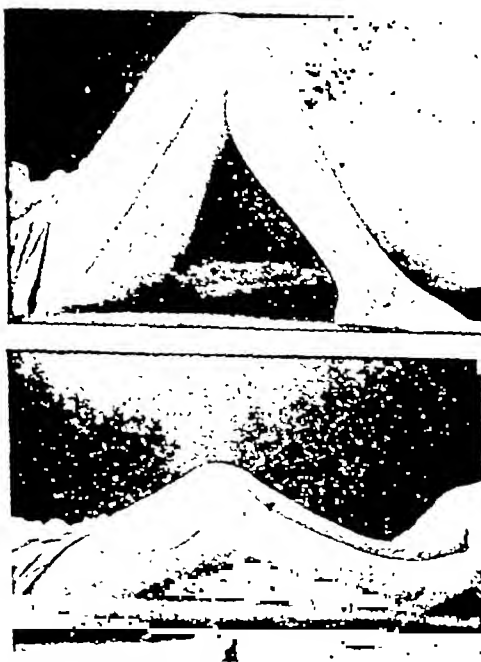


Fig. 111.—Case 2. Arthritic contractures of both knees. Range of motion before operation. (Long scar from incision of removal of fascia for arthroplasty of elbow.)

not one but several operations must be performed in order to obtain relief. These must be done at properly spaced intervals, and each carried through with its appropriate after-treatment before the goal is attained. Each link must be forged separately and then welded together before the chain is complete, and one defective link may mean the failure of the entire chain. Nevertheless what has been done for some can also be done for others. Helpless arthritic cripples have been trans-

formed into active, independent individuals, in some instances able to contribute to the income of the family. Improvement of greater or lesser extent may be obtained in a large number of properly selected arthritic invalids.

The surgeon must attempt to answer the following questions in relation to the individual patient:

1. Is the arthritis quiescent?
2. Is the patient's physical condition good enough to warrant undertaking an extensive surgical program?
3. Is the expected functional gain likely to be worth the effort, taking into consideration the patient's age, physical condition, and the series of operations necessary?
4. Is anything to be gained by delaying the operation and by advising further treatment of any kind?
5. Are the patient's morale and willingness to stand pain such as to offer promise of the necessary cooperation in the after-treatment?
6. Does the hospital where the patient is to be treated possess all the necessary facilities for successful treatment?
7. Can arrangements be made for the necessary treatment and surgical supervision after the patient leaves the hospital?
8. Has the patient provided an adequate budget to see the treatment through from beginning to end? (Under present conditions often an insurmountable obstacle.)

**Surgical Objective.**—The surgeon must have a clear idea of the objective in view and must not be led away from the pursuit of one goal to that of another before the first is reached. On account of the great variation both in the extent of the involvement and in the joints that are principally affected, this is likely to happen unless he clearly differentiates the arm problem from the leg problem:

1. The arm problem has to do with restoring the use of the arms and particularly to permit the patient to eat, dress and perform the various acts of toilet and personal care without assistance. When the elbows are ankylosed and the fingers and wrists stiff, the patient is practically as helpless as if both arms had been amputated and, if possible, relief should be given.

2. The leg problem has to do with restoring the patient's ability to move about without assistance. It is not sufficient

only to restore the power of locomotion but the patient must also be able to get up from a chair and to sit down again unaided.

The solution of either of these problems constitutes an end in itself and the gain justifies the series of procedures which may be necessary. When both the arms and the legs are disabled, the solution of the arm problem should be attempted first and the effort is justified even though nothing be attempted for the legs. The surgeon must avoid operations that do not



Fig 112.—Case 2. After posterior capsuloplasty of both knees.

lead to either one or the other of these goals and that might prove of theoretical or esthetic benefit only.

**When to Operate.**—It needs to be emphasized again, for fear of misunderstanding, that the rôle of surgery in the treatment of chronic atrophic arthritis comes only after the disease has reached a stage of quiescence and has remained so for at least six months. Even this is too short a time to be free from the danger of recurrence, but if this does occur there is likelihood that it can be held in check by proper treatment. Physicians must learn to differentiate the inactive from the active stage. In many cases this is easy from the history and the

examination; in other cases it may be difficult. The chief cause of error is the persistence of pain, the physician being unable to differentiate the pain caused by stretching of adhesions, movement of a fibrosed capsule, or strain resulting from attempted use of a damaged joint from that caused by actual arthritic swelling and inflammation. Careful examination of the joint and analysis of the maneuvers that reproduce the pain will usually yield evidence upon which an opinion may be formed. When doubt persists the matter can only be determined by observation over a period of time.



Fig. 113.—Case 3. Multiple atrophic arthritis. Motion in right elbow following arthroplasty.

**Operative Procedures.**—A variety of operative procedures may be employed for the relief of the disabilities of atrophic arthritis. These include synovectomy, capsuloplasty, osteotomy, arthrodesis and arthroplasty. The selection of the appropriate procedure depends upon the estimation of the nature and severity of the pathologic changes in the affected joint and upon the appraisal of the patient as an operative risk. The strain of an operation is in some ways akin to that of participating in an athletic contest and no patient who has been inactive for years is a good operative risk. Minimal procedures should be selected and one should avoid the mistake of attempting more than one operation at a time. Nevertheless, it is

impossible to avoid all danger in the rehabilitation of the arthritic cripple and one is sometimes confronted by the alternative either of going ahead at considerable risk or of abandoning the attempt altogether. In such a case the decision should be left to the patient after frankly presenting both sides of the question to him.

**Synovial Hypertrophy.**—Hyperplasia of the synovial membrane is a characteristic part of the pathologic process of atrophic arthritis and may persist even after the disease has become inactive and constitute a cause of disability. The membrane becomes thickened and is thrown into folds and villi which may cause mechanical interference with joint function or become pinched between the articular surfaces with the production of pain. Synovial hypertrophy is not infrequently associated with chronic effusion or hydrops, the scarred and thickened membrane not permitting the normal drainage or interchange of fluids. The condition is seen most typically in the knee joint where, because of the large synovial area and the superficial position, it is more evidently a cause of trouble than elsewhere.

Tenderness in the region of the infrapatellar fat pad, pain and restriction of motion on attempt to completely extend the knee, are not infrequent symptoms. Upon x-ray examination the joint cartilage shows no damage or only slight damage and the changes are chiefly thickening of the soft parts.

In such cases when supportive measures have been tried without result, relief may be obtained by the operation of synovectomy. It has been shown by experiments upon animals that excision of the synovial membrane is followed by the formation of a new synovial layer developed by metaplasia of the surrounding connective tissue. The operation should be performed cautiously and only in selected cases as experience has shown that when performed indiscriminately there may be a diminution of joint motion or a recurrence of pain. I have not been impressed from observation of my own and other surgeons' cases that there is any evidence to support the claim that synovectomy rids the body of a focus of infection which may serve to propagate the disease in other joints.

Postoperative splinting is not generally required after synovectomy, large compression dressings being sufficient. Active

movement is encouraged beginning a few days after operation. Weight bearing is usually permitted at the end of three to seven weeks.

**Flexion Deformities of the Joints.**—Joint deformities in atrophic arthritis are chiefly the result of the patient's efforts to obtain relief of pain during the active stage of the disease by flexing the joints and maintaining them in positions of relaxation. Complete extension, because it puts tension upon the ligaments, is the more painful motion and the one that is chiefly avoided. The joint capsule which is thickened and infiltrated adapts itself to the flexed position and loses its exten-

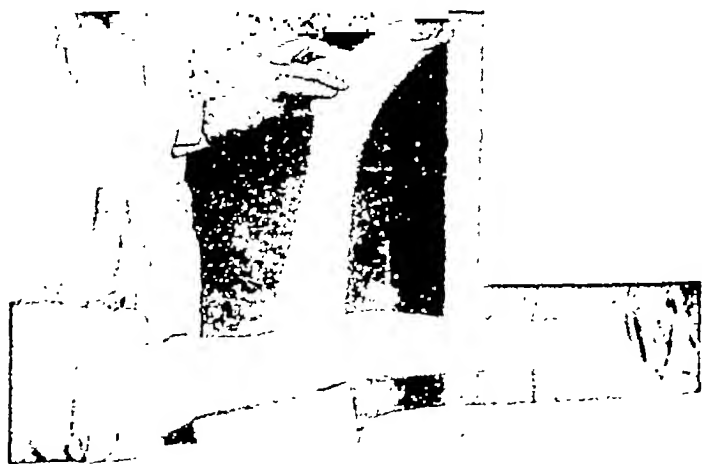


Fig. 114.—Case 3. Motion in left knee following arthroplasty.

sibility; the muscles become contracted, and unless measures are taken to overcome it the deformity becomes fixed. The longer it is allowed to persist, the more permanent the character of the contraction. If the arthritis becomes inactive and healing occurs without much articular damage, the joint still remains partially flexed because of fibrotic changes in the capsule. If the arthritic process continues the articular cartilage is destroyed, the synovial pouches become obliterated and adhesions form between the layers of pannus covering the ends of the bones. The joint still remains flexed but there is now a condition of fibrous ankylosis and in time this may go on to bony ankylosis.

It is necessary to point out that flexion deformities of the joints almost always represent errors and neglect of previous treatment. While one must admit that the difficulties in the way of prevention are many in a disease like atrophic arthritis, which lasts through many years and eventually passes through a good many different medical hands, they are not insurmountable if every physician having to do with the condition exercises the necessary foresight. The removal of pillows from under knees, the use of adhesive extension from time to time to the



FIG. 115.—Case 3. x-Ray following arthroplasty of left knee.

legs, or part time splinting will prevent the need for later surgery in many of these cases.

**Capsular Contraction.**—Simple capsular contraction with but slight damage to the joint cartilage is most frequently a cause of disability in the elbows and knees. In the elbow the contracture shows itself chiefly as a limitation of extension but does not cause any great handicap as long as motion in flexion is preserved because of the fact that the arm is used chiefly with the elbow flexed. In the case of the knees, however, complete extension is necessary for locomotion and to relieve the extensor muscles of too great a burden when weight

is borne. Flexion contractures of the knees are usually bilateral and when they exceed 30 degrees usually drive the patient to a wheel chair existence.

The characteristic feature of these contractures is the preservation of motion in flexion so that the joint may be bent almost to the normal limit. It cannot be extended, however, beyond a certain fixed point. There is frequently a certain amount of posterior subluxation of the tibia on the femur but the x-ray examination shows only slight if any changes in the articular cartilage.

Numerous procedures have been devised to overcome these flexion contractures of the knees, mostly in the form of special appliances exerting traction or leverage on the leg in such a manner as not only to correct the flexion but also to overcome the posterior subluxation of the tibia. They necessitate prolonged fixation of the joint which is always unwise in atrophic arthritis even in the quiescent stage. Such gain as is made in extension is usually won at the cost of pressure sores in the heels, circulatory disturbance of the feet and decreased motion of the knees. Manipulative correction is a dangerous procedure even when done gently and may easily result in a fracture because of the extreme atrophy and fragility of the bones. In the quiescent stage it is rarely advisable because of the long-standing and fixed character of the deformities and in the end open procedures are generally to be preferred.

After trial of many of these methods I became dissatisfied with their results and more than ten years ago began to resort to operative freeing of the capsule. This operation has given good results in properly selected cases and I have continued to use it. The technic of this operation has been described under the name of posterior capsuloplasty and, in brief, consists of making an incision over the lateral aspect of the knee, dividing the iliotibial band of the fascia lata, lengthening the biceps tendon, both of these structures being contracted, and then opening the posterior compartment of the knee and stripping away the attachments of the posterior capsular ligaments to the femur. It is then usually possible to manipulate the knee into complete extension in which case after closure of the incision a plaster casting is applied. Otherwise extension is applied by means of a wire passed through the os calcis.



Since only the soft parts are sectioned during the operation, it is possible to begin movement at the end of two to three weeks. The casing is split and removed during the daytime to permit exercise but is reapplied at night. Walking with a brace is permitted at the end of four to five weeks. The use of a night plaster is continued for upward of six months in order to prevent any danger of a recurrence of the contracture.

**Capsular Contraction with Joint Damage.**—When the arthritis has progressed a stage farther than that just described



FIG. 116.—Case 4 Bony ankylosis of both hips. Patient unable to sit, stand or walk with any comfort.

the treatment becomes more complicated because of the added factor of considerable articular damage. Here again such deformities are of chief interest in relation to the knees because the largest gain is to be obtained from their correction. Examination of such knees shows a smaller amount of free motion than in the simple capsular contractions and the restriction is not only in extension but also to a lesser degree in flexion. The motion may be free from pain and of sufficient extent to be useful if it only occurred in an arc where it would be of greater functional value. The x-ray examination generally reveals

narrowing of the joint space but the amount of cartilaginous damage is not extreme.

On the whole, the simplest solution of this problem is to perform a supracondylar osteotomy of the femur and to secure complete extension of the knee at the cost of angulating the femoral fragments. The drawback to this operation is that it requires eight weeks' immobilization in plaster and, as pointed out previously, is likely to be attended by some diminution in the range of motion. This has been confirmed to a certain extent by the experience with certain cases and while the decrease has not been serious it has led me to be cautious and to restrict the use of osteotomy to deformities in which the indications are very definite.

**Painful Joints.**—Extensive damage to the joint cartilage may of itself be a cause of painful function without necessarily causing marked limitation of joint motion. Pain of this type is incurred only on use of the joint and is relieved promptly by rest. If the patient persists in using the joint there is reaction in the form of swelling and effusion. Clinical examination might easily lead one to conclude that the trouble was due to proliferation and thickening of the synovial membrane but the cue to the real difficulty is obtained from the *x*-ray examination which shows extensive changes in the articular surfaces. There is narrowing of the cartilage space, irregularity and eburnation of the bony surfaces and considerable productive change of the joint margins. Such pathologic changes are incompatible with good joint function and one is justified in considering a surgical remedy. Too often under these circumstances the surgeon jumps to the conclusion that fusion of the painful joint offers the best solution.

I do not agree with this opinion, and in general believe the resort to fusion operations in atrophic arthritis is ill advised. This disease is subject to recurrences of activity from time to time and one can never predict with certainty that other joints may not be involved at some later time. One should always aim to preserve or increase motion in arthritis instead of eliminating it. I have frequently seen arthritic cripples in whom the reconstructing problem was rendered infinitely more difficult because of a previous fusion operation. The articulations adjacent to the fused joint are rarely normal and the

patients have usually walked awkwardly and used the limbs poorly. I have fused some arthritic knees but have never done it without later regrets.

Painful joints must be relieved but this can usually be accomplished in other ways than by fusion. The cause of the pain must be carefully sought. If due to synovial hypertrophy or tabs, partial or complete synovectomy may be the remedy. If the result of ligamentous strain, the faulty weight-bearing lines should be corrected and the limb adjusted in proper position. This may necessitate the use of various types of braces



Fig 117.—Case 4 Robert Jones' pseudarthrosis of both hips. Motion restored.

or the performance of an osteotomy. If it is due to articular damage, then partial or complete arthroplasty may be required.

**Ankylosis.**—Ankylosis of one or several joints is the common late result of unchecked atrophic arthritis. With the development of multiple ankyloses, the active arthritis usually is extinguished as if it lacked further fuel to keep it burning. The patients are completely helpless and dependent and the effect is the same whether the ankylosis is fibrous or bony. The only remedy for ankylosis is the operation of arthroplasty, and in these ossified cripples not one but several arthroplasties may be required if worth-while results are to be obtained.

Arthroplasty is an operation to construct a new joint. If bony ankylosis is present the bones are divided at the level of the old joint, the ends trimmed and smoothed to simulate the normal articular configuration and the surfaces are then covered with a sheet of fascia lata removed from the thigh and carefully stitched in place. If the ankylosis is fibrous the joint surfaces are removed and fascia lata interposed in exactly similar manner. The fascia serves a double purpose; first, of preventing recurrence of ankylosis by forming an intervening barrier between the raw bone ends, and, secondly, of forming



Fig. 118.—Case 4. Range of abduction following Jones' pseudarthrosis

the foundation for the development of a pseudarthrosis such as is seen when a fracture fails to unite by providing a nidus of fibrous tissue from which granulation tissue grows to obliterate the joint space. Different methods must be employed to deal with the different joints but it is unnecessary to bother you with details of operative technic or to explain the individual variations of different surgeons, as I am chiefly concerned with showing what may be done. It is sufficient to state that prolonged and patient after-care is necessary, which requires the full cooperation and determination of the patient and that with-

out these the result may be failure, irrespective of how skillfully the operation is performed.

My first operations for the relief of ankylosis in atrophic arthritis were performed approximately fifteen years ago and were accompanied by misgivings because of the warnings of experienced surgeons that such operations were inadvisable in this disease. Tragedies have not resulted; there have been but few complete failures and on the whole the results have exceeded expectations. This experience has tended to make me broaden the indications for its use and I do not hesitate to advise it now in cases which I would not have considered operable by former standards. Even when there is later recurrence of the arthritis the new joint produced by arthroplasty retains its good function and shows no evidence of involvement. The elbow and jaw give the best results, the knee the next best, and the hip follows closely after. Weight bearing after arthroplasty of the knee or hip should be postponed until the end of twelve weeks and then only with brace protection. Arthroplasty of the finger joints is a tedious procedure but worth-while results can be obtained when it is performed with proper technic.

Multiple arthroplasties have been performed at different times in the same patients with, in some instances, remarkable functional improvement. In case of bilateral ankylosis of the elbows double arthroplasty may be counted upon to give good results. In case of bilateral ankylosis of the knees it is usually sufficient to perform arthroplasty of a single knee although in 2 patients I have done double arthroplasty with fair results. In case of ankylosis of both hips double arthroplasty is frequently necessary, and I have seen the result in the first hip improved after doing the second. In case of ankylosis of both hips and both knees the attempt should be made to restore motion in one hip and in the opposite knee. Later it can be decided whether something should be attempted for the second hip.

In a complicated problem of this type Jones' operation for creating a pseudarthrosis of the hip presents certain advantages. The neck of the femur is divided at its base and the greater trochanter with its attached muscles is split off and turned up to cover the raw bone surface of the neck after the

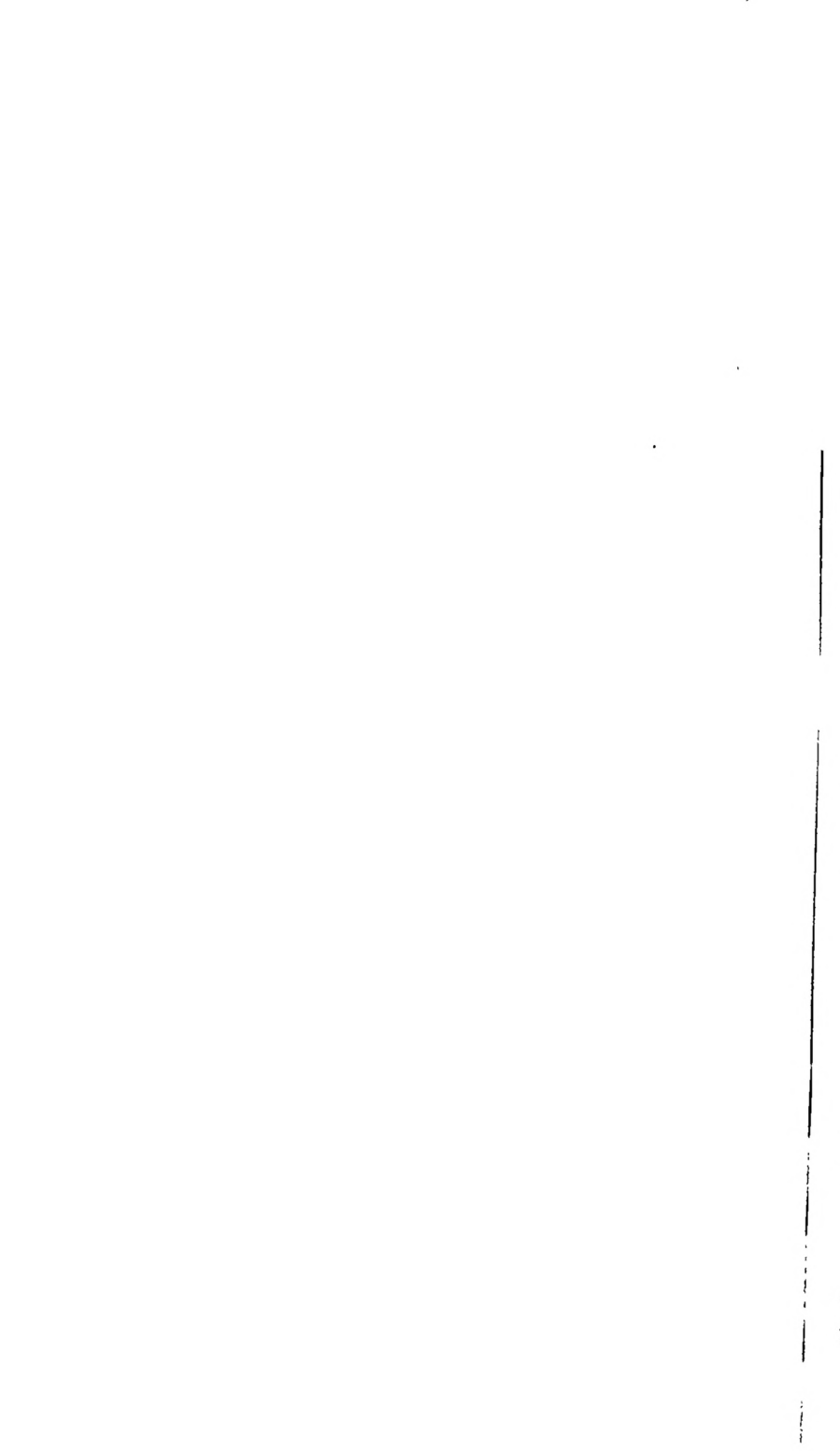
excision of a generous portion of the bone.' The neck thus serves as a buttress or shelf to prevent upward displacement of the shaft. The operation may be depended upon to restore movement of the hips although at the expense of some loss of stability.

**Conclusion.**—In what has gone before I have tried to sum up clinical impressions obtained from the study of a group of more than 125 patients with approximately 200 operations performed in the last fifteen years. I have attempted to show that surgical measures are frequently required to carry on, and complete the work of rehabilitation of the arthritic cripple, but that the field of surgery is strictly limited and should never begin until after the disease has been rendered inactive by general medical treatment. The treatment is costly both in time and effort but worth-while rewards are obtained when patients may again begin to take care of themselves or may leave their wheel chairs and begin to walk. It is for the physician to learn the possibilities of surgical reconstruction and to open up for many patients new avenues of hope.

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## CLINIC OF DR. SOLOMON FINEMAN

SEA VIEW AND MT. SINAI HOSPITALS

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### THE RÔLE OF THE ROENTGENOLOGIST IN THE DIAGNOSIS AND TREATMENT OF CHRONIC ARTHRITIS

The chronic arthritides form the following 9 clinical groups:

1. Atrophic. Synonyms: rheumatoid, chronic infectious of unknown etiology, proliferative.

In this group belong the arthritides discussed by various authors under the following names: chronic polyarthritis, ankylosing polyarthritis, nonspecific nonsuppurative focal arthritis deformans, spondylarthritis, spondylarthritis ankylopoietica, ankylosing spondylitis, spondylitis ossificans ligamentosa, spondyloze rhizomêlique, Marie-Strümpell disease, Pierre-Marie-Strümpell disease, spondylitis muscularis (Bechterew type), spondylitis senilis, and juvenile polyarthritis (Still's disease).

2. Hypertrophic. Synonyms: osteo-arthritis, degenerative or senescent, non-ankylosing.

In this group belong spondylitis deformans, Schmorl's deforming spondylosis, spondylosis deformans, morbus coxae senilis, Heberden's nodes, and osteochondritis desiccans.

3. Mixed, atrophic (rheumatoid) and hypertrophic (osteo-arthritis) arthritis occurring in the same patient.

4. Specific infectious: gonorrheal, syphilitic, tuberculous, typhoid, pneumococcic, staphylococcic, streptococcic, meningococcic, influenzal, and those due to trichinosis or dysentery bacillus infections.

5. Neuropathic: Charcot joint, syringomyelia, and posthemiplegic.

- 6 Joint changes due to faulty constitutional processes as seen in gout, scurvy, hemophilia, serum allergy, intermittent hydrarthrosis, Paget's disease, hyperparathyroidism, food allergy, climacteric, ovarian and thyroid disturbances.

- 7 Traumatic: endogenous or exogenous.

- 8 Neoplastic: benign, primary malignant, and metastatic.

- 9 Unclassified

### ROENTGENOLOGIC DIFFICULTIES IN CLASSIFYING ARTHRITIS

It is well to remember that clinical arthritis even though of long standing may not show roentgen evidence of joint change in many cases. The disease process may be limited to

the soft tissues and the changes may be insufficiently pronounced to be visible on the roentgenogram.

In typical atrophic (rheumatoid) arthritis, the following changes occur early and can be recognized roentgenologically: proliferation of the synovial membrane, thickening of the joint capsule, and joint effusion may become apparent as increased density of the soft tissues, with visible distention of the joint capsule and displacement in the knee, for example, of such joint structures as the fat pads and patella.

Later there occurs atrophy of the bony tissues adjacent to the joint with partial or total destruction of the cartilage, and consequent narrowing or obliteration of the joint space. Erosion or marked destruction of the articular bony margin, with formation of loose bodies occasionally, and with partial or complete dislocation of the articulating bones may follow. The end-result is fibrous or bony ankylosis. This constitutes the classical roentgen evidence of atrophic (rheumatoid) arthritis.

In atrophic (rheumatoid) spondylitis there occur, early, irregular calcifications of the ligaments. The process may progress, resulting in bony ankylosis of the entire spine. The intervertebral disks may be somewhat narrowed but they are not destroyed. The vertebral bodies show atrophic changes, and often lipping. The articulating facets may show atrophic changes and may fuse.

In typical hypertrophic arthritis (osteo-arthritis), the early roentgen changes are seen as increased densities due to localized synovial membrane proliferations. There may be slight periarticular lipping and slight atrophy of the cancellous bone close to the joint. Later the lipping becomes more prominent, and the joint space usually shows some narrowing. Later on the joint space may be completely obliterated with approximation of the bony surfaces. This depends on the degree of cartilaginous destruction. Hyperostosis, with pronounced spur formation is common, occasional bony bridging occurs. The articular bone shows sclerosis and may later show erosions of the articular surface with cystic destruction of the cancellous bone. Loose bodies, due to detached periarticular chondro-osteophytes, may be seen. Subluxation may occur as well as calcification of the joint capsule and ossifying periostitis of the shaft near the joint. In rare cases ankylosis occurs.

In hypertrophic spondylitis (osteo-arthritis) the ligaments do not usually calcify. The vertebral bodies are not destroyed but on the contrary show increased sclerosis. Bony spurs form early, and are prominent, and segments of the spine may be fixed by mechanical interlocking of the exostoses. The intervertebral disks show destructive changes. The facet spaces show narrowing and there is sclerosis of the articular facets.

The chronic arthritides of the mixed group show a mixture of the roentgen changes described under the atrophic (rheumatoid) and hypertrophic (osteo-arthritic) form of arthritis. The changes of one type may predominate and almost completely mask the other type. Often the picture is extremely confusing.

The arthritides of the remaining groups, with the exception of joint neoplasms, show the same basic roentgen changes. They do not present characteristic pathognomonic findings. The changes may be atrophic, hypertrophic or both depending on the duration of the disease, the joint involved, the age of the patient and many other factors. In chronic arthritis of every type the roentgenologist is often faced with insuperable difficulties when he attempts etiologic classification solely on the basis of roentgen findings. The pitfalls are numerous and mistakes in diagnosis are frequent.

Some of the inherent difficulties of the subject may become evident from the following review of the literature:

Two types of arthritis may be present in one and the same patient (Scott, 1932<sup>1</sup>).

Spackman<sup>2</sup> (1936) states that "as pointed out by Osgood and others we can not say that both processes (atrophic and hypertrophic arthritis) do not occur simultaneously in the same patient or even in the same joint."

Rigler and Wetherby<sup>3</sup> (1933) failed to observe, in their group of cases, hypertrophic changes in any elbow or shoulder, and only few spine and knee cases with atrophic changes. They suggest that the type of joint reaction may be due to location rather than to its etiology. In 21 per cent of the joints which had been afflicted more than five years there were no roentgenographic abnormal changes. A negative roentgenogram even late in the disease is of little significance.

There are cases on record in which roentgenograms were made early in the process and the condition classified as atrophic

arthritis, and in which later the diagnosis was changed to hypertrophic or mixed arthritis (Wetherby,<sup>4</sup> 1932).

The end-stage of both atrophic and hypertrophic arthritis may be bony ankylosis (Osgood,<sup>5</sup> 1930; Baetjer and Waters,<sup>6</sup> 1921).

Osgood<sup>5</sup> (1930) believes that occasionally both atrophic and hypertrophic arthritis may exist in the same patient, though this is relatively rare.

Brailsford<sup>7</sup> (1935) calls attention to the fact that the shoulder joint is subject to rheumatoid (atrophic) arthritis, but relatively rarely to osteo-arthritic (hypertrophic) changes.

Wetherby<sup>4</sup> (1932) calls attention to the fact that the shoulder joint, for instance, shows in nearly all cases atrophic changes, while in the knee hypertrophic changes are much more common. He stresses the significance of this in view of the involvement of the knee and shoulders, in arthritic persons of all age groups, in about the same incidence.

Localized atrophic arthritis (rheumatoid) of the spine which frequently responds to removal of foci of infection (teeth, sinuses, gallbladder and gastro-intestinal tract), may later show lipping of the margins, pointing of the articular facets, ossification of the anterior ligaments, destruction of one or more intervertebral disks and irregularity and sclerosis of the opposing vertebral surfaces (Brailsford,<sup>7</sup> 1935).

Rigler and Wetherby<sup>3</sup> (1933) conclude that the end-result of the proliferative form of arthritis (atrophic) is a combined destructive and hypertrophic reaction.

Doub<sup>8</sup> (1936) points out that atrophic and hypertrophic arthritis are frequently seen as mixed types, and it is often difficult to say which type antedated the other. In some cases it is also difficult to distinguish between the two types from pathologic specimens either by gross or microscopic examination. They are also in some instances indistinguishable from other types of arthritis at certain stages of their course.

In many cases there is grafting of one form of arthritis on the other, as for example where fusion of bones with ankylosis is found associated with well-developed spurs in which bony trabeculae are plainly visible. In other cases predominant hypertrophic changes in certain joints and unmistakable signs of atrophic changes in other joints were found in the same patient (Spackman,<sup>2</sup> 1935).

Allison and Ghormley<sup>9</sup> (1931) found in their study of joints by gross and microscopic examination that the distinction between the proliferative (atrophic) and degenerative (hypertrophic) forms was not always distinct.

Changes in joints due to various etiologic agents at times simulate each other (Wetherby,<sup>4</sup> 1932).

A typical case of atrophic arthritis (spondylitis deformans of the Marie-Strümpell type) may be indistinguishable from a gonorrheal infection (Knaggs,<sup>10</sup> 1925).

Hypertrophic arthritis (osteo-arthritis) may simulate in old persons the reparative stage of tuberculous, gonorrheal, syphilitic and pneumococcic arthritis (Gelber,<sup>11</sup> 1934).

Pepper<sup>12</sup> (1929) describes a chronic deforming gonorrheal arthritis with both hypertrophic and atrophic changes which is not to be differentiated as to cause from the roentgenograms alone. He also describes a type of gonorrheal arthritis with punched-out areas in the bone which resembles gout. He concludes by stating that gonococcal arthritis does not present a distinct roentgen appearance, but that the roentgenogram used in conjunction with the history may be of valuable diagnostic assistance.

Shapiro<sup>13</sup> (1932) and Rigler and Wetherby<sup>3</sup> (1933) state that gonorrheal arthritis may be indistinguishable from atrophic arthritis.

Charcot's hip and shoulder joints and spine may show atrophic and hypertrophic phases. The atrophic type may be simulated by tuberculosis of the spine (Brailsford,<sup>7</sup> 1935).

Baetjer and Waters<sup>6</sup> (1921) emphasize that in tuberculous spondylitis there is no evidence of new bone production.

In contradiction of Baetjer and Waters' statement that new bone formation does not occur in tuberculous spondylitis, and despite this general belief, areas of new bone production around tuberculous vertebrae are not uncommon. In rare cases tuberculous spondylitis may imitate deforming spondylosis (hypertrophic) (Freedman,<sup>14</sup> 1934).

In old age, tuberculous arthritis may be mistaken for septic or hypertrophic arthritis (Holmes and Ruggles,<sup>15</sup> 1936).

Pomeranz<sup>16</sup> (1933) states that contrary to opinion an early or positive diagnosis in tuberculous arthritis is no easy task, and that an accurate interpretation is extremely difficult. The

roentgenogram is but a record of the disease at a given moment. Synovitis, periarticular swelling and atrophy of bone are common to all arthritides, and are of limited value in the diagnosis of tuberculous arthritis. Atrophy of the bone is usually marked, but sclerosis and bone production occur in tuberculosis, even in the absence of a mixed infection.

The punched-out areas in the epiphyses representing the presence of tophi, are not pathognomonic for gout. They are often present in atrophic arthritis (chronic proliferative, rheumatoid) (Wyatt,<sup>17</sup> 1933).

Holmes and Ruggles<sup>15</sup> (1936) state that in early stages of gout it may be mistaken for hypertrophic arthritis. With reference to tuberculous arthritis they write that in old age the disease may be mistaken for septic or hypertrophic arthritis.

Shapiro<sup>13</sup> (1932) claims that the supposedly typical punched-out areas of bone in gout are commonly seen in atrophic arthritis.

The cavities noted in the head and neck of the femur in many of the so-called "osteo-arthritic hips" (hypertrophic) may be of gouty origin. When gout attacks a major joint there are no radiographic changes of diagnostic value (Scott,<sup>1</sup> 1932).

Hench<sup>10</sup> (1937) writes that he is unaware of any proved case of gouty spondylitis in the literature for many years. It has been his experience that acute gout practically never involves joints of the torso, namely, those of the spinal column, hips and shoulders. Thannhauser, Pratt, Monroe and Lichtwitz (quoted by Hench) had never noted spinal involvement in any of their cases of gout. Monroe and Lichtwitz had never, and Thannhauser had rarely encountered involvement of the hips. However, Talbot (quoted by Hench) had under observation a patient with tophaceous gout and gouty arthritis of several joints whose roentgenograms gave evidence of gouty erosion in the sacro-iliac joints, and Bauer stated that on postmortem examination recently he had found urate deposits in the vertebrae of 1 case.

Keefer and Myers<sup>20</sup> (1933) write that there is no absolutely characteristic picture present in all cases of hemophilic arthritis. The chronic lesions may resemble gout, degenerative (hypertrophic), or tuberculous arthritis (Doub,<sup>8</sup> 1935). Late

in hemophilic arthritis roentgenograms may simulate those in tuberculous, atrophic or other types of arthritis (Kahn, Rypins, Solis-Cohen and Levine, quoted by Hench<sup>18</sup>).

Doub and Davidson<sup>21</sup> (1926) say that in early hemophilic arthritis there are no destructive changes. In these cases there is effusion of blood into the joint, thickening of the joint capsule, and lipping similar to hypertrophic arthritis. In the advanced stages there are destructive changes both in the joint cartilage and bone. There may be punched-out areas in the epiphysis, destruction of the articular surface and blood in the synovial cavity.

In traumatic arthritis the picture of capsular distention due to increase of synovial fluid differs little from the first stage of an infectious process of known etiology. If continued over a long time, destructive and productive changes occur in the same joint (Gelber,<sup>11</sup> 1934).

The changes in traumatic arthritis, due to injury are synovial thickening, necrosis of the cartilage, with narrowing of the joint space and bone proliferation. This type of arthritis simulates hypertrophic arthritis (osteo-arthritis), and it is difficult to distinguish the two types roentgenographically (Doub,<sup>22</sup> 1933).

It should be evident from this survey that precise classification of the arthritides based solely on roentgenographic evidence is too often unsatisfactory to be of much aid to the clinician.

Rigler and Wetherby<sup>3</sup> (1933) in their study of 60 cases of chronic polyarticular arthritis observed that a large number of arthritic joints may give no abnormal roentgen findings throughout the course of the disease. They attempted to divide their cases roentgenologically into "atrophic," "hypertrophic" and "infectious" groups. Most of the infectious cases occurred in the later decades of life and with the greater duration of the disease, indicating to the authors that the combined destructive and hypertrophic reaction of the "infectious" type is simply a more extreme and older phase of atrophic arthritis. They concluded that roentgenologic attempts to differentiate between atrophic and "infectious" arthritis should be abandoned, and that for roentgen purposes chronic arthritis should be divided into atrophic, hypertrophic and mixed.

Scott<sup>23</sup> (1935), however, divides the hypertrophic type of arthritic cases into infectious and noninfectious groups, the basic differences in his classification of joints being as follows: (1) decalcification of the skeleton is peculiar to rheumatoid arthritis, (2) loss of cartilage with the formation of osteophytes is associated with the osteo-arthritic group, (3) loss of cartilage with early sclerosis of those bones entering into the formation of the joint, usually of a single finger, denotes a chronic infective arthritis, while (4) the "punched-out" areas seen on the edge of the articular surfaces indicates the presence of gouty deposits, which are characteristic of gouty arthritis. He reminds us, however, that it is possible to get a mixed or dual arthritis, or even 3 types of arthritis in a single patient.

Aldred-Brown and Steven<sup>24</sup> (1936) attempted to follow Scott's classification in 154 consecutive cases but did not feel justified in separating cases of rheumatoid arthritis from those of chronic infective arthritis. Strangeways<sup>25</sup> concluded long after many years of investigation that it was impossible by any known method, including the radiologic, to distinguish between the different types of arthritis. Hench (1936) regards Gelber and Goldberg's roentgenologic classification into "infectious" and "atrophic" as unnecessary. Spackman<sup>2</sup> (1936) writes that the roentgenologist in interpreting his findings must weigh and consider carefully both the clinical and the roentgen features of the particular case in question. Otherwise the result is too often a roentgenologic report which is not only of no direct assistance to the physician but may be grossly misleading. Occasionally he has not been able to decide from the roentgen evidence alone whether the hypertrophic or atrophic variety is present. The roentgenologist should not be guided solely by those changes which he can see on the roentgenograms.

Wyatt<sup>17</sup> (1933) states that the pathology of early atrophic arthritis explains the absence of early roentgen findings other than those that characterize the beginning of all joint disease. Formerly it was considered the function of the roentgenologist to confirm diagnoses of tuberculosis of the hips, spine and so on, but such is no longer the case.

Many others admit that attempts to classify the arthritides on purely roentgenologic data lead to failure and often misguide the clinician. Among this group we may name Moore<sup>26</sup>



(1929), Wetherby (1932), Morrison and Kuhns<sup>27</sup> (1936). Fisher<sup>28</sup> (1936), and Holmes and Ruggles<sup>15</sup> (1936). Most of the literature alludes to the great help obtained by the roentgen method of examination; some even state that the exact type of arthritis can be ascertained in this way but that this is true only in some cases.

#### DIFFICULTIES IN DETERMINING THE ETIOLOGY OF ATROPHIC (RHEUMATOID) AND HYPERTROPHIC ARTHRITIS (OSTEO-ARTHRITIS)

It is generally admitted that the exact etiologic agent or agents responsible for the atrophic and hypertrophic forms of arthritis are unknown. Spackman<sup>2</sup> (1935), Morrison and Kuhns<sup>27</sup> (1936) suggest the possibility of common unknown etiologic factors affecting joints differently at different age levels under different metabolic or endocrine conditions. Morrison and Kuhns<sup>27</sup> (1936) state that the belief has wide acceptance that both the atrophic (rheumatoid) and hypertrophic (osteo-arthritis) forms of chronic arthritis are often the result of similar etiologic factors. Both types may show increased density or decreased density of bone, particularly in the mixed forms of arthritis. Localized decalcification and apparent cyst formation are often observed about the metacarpal and phalangeal joints of both types of arthritis. In the past too much emphasis has been placed on the roentgenogram alone. In adult life and in the aged the differentiation of types of chronic arthritis becomes increasingly difficult. The roentgen changes, commonly called the manifestations of atrophic or hypertrophic arthritis, were frequently found to merge.

Steindler<sup>29</sup> in a study of 4339 cases of chronic arthritis of the atrophic (rheumatoid) and hypertrophic (osteo-arthritis) types found surprising relief for the first year in 20 per cent and a maintained relief in 8 per cent of the chronic hypertrophic arthritis (osteo-arthritis) cases following removal of foci of infection.

Miltner and Kulowski<sup>30</sup> (1933) considered the teeth, tonsils, paranasal sinuses, gastro-intestinal tract, genito-urinary tract and the mastoids as foci in their study of 100 cases of atrophic (rheumatoid) and of 100 cases of hypertrophic arthritis (osteo-arthritis).

In his paper on the radiographic dissection of chronic rheumatic arthritis, Scott<sup>1</sup> (1932) writes that many of the cases of spondylitis deformans (hypertrophic arthritis) show evidence of chronic infective condition or even abscess formation in the sacro-iliac joints.

In the recent British classification of arthritis one notes that hypertrophic arthritis (osteo-arthritis) may be associated with infection, that it may be secondary to atrophic arthritis (rheumatoid), that it may be secondary to trauma, or that it may be associated with disordered metabolism (climacteric, gouty, scurvy, hemophilia), or associated with organic diseases of the nervous system as in Charcot's joints or syringomyelia (Fisher,<sup>28</sup> 1936).

Miller<sup>31</sup> favors the term "osteo-arthrosis" for hypertrophic (senescent, degenerative) arthritis, to indicate lack of an infective factor in this pathologic process.

Schauffler<sup>32</sup> (1927) believes that hypertrophic arthritis is not caused by bacterial invasion and is not cured by removal of foci of infection. In his opinion the products of bacterial growth in the colon may influence the development of hypertrophic arthritis.

In 1000 consecutive cases of "lumbago" or "sciatica" Brailsford<sup>33</sup> (1932) found definite evidence of hidden sepsis in 682.

It is evident from reviewing the literature on the roentgen classification of the atrophic (rheumatoid) and hypertrophic (osteo-arthritic) forms of arthritis that the roentgenologist may find great difficulty very often in differentiating between these two disease processes.

It is also well known that the clinical differentiation between these two forms of chronic arthritis is often extremely difficult. It is clinically very important, however, to know whether the atrophic (rheumatoid) factor constitutes part of the picture in a patient with chronic arthritis, because the type of treatment chosen is often largely dependent on this clinical point.

The great difficulty in all clinical efforts to classify chronic arthritis is due to the fact that at the moment there is not available a single specific test for differentiating between atrophic and hypertrophic arthritis. The increased sedimenta-

tion rate of the red blood cells is said to be the most reliable test in the atrophic form of arthritis (Short, Dienes, and Bauer,<sup>34</sup> 1937). This test cannot be used, however, to differentiate atrophic (rheumatoid) from hypertrophic arthritis (osteo-arthritis).

As a result of this difficulty clinicians have developed a tendency to utilize to a large degree the roentgenologic examination of the joints for classification of the arthritides. Wetherby<sup>4</sup> (1932) wrote that often diagnosis of the type of arthritis present is withheld until the report on the roentgen examination is available, and then the diagnosis is made according to the changes seen in the roentgenogram.

In the writer's experience, covering a period of twelve years, during which time he has worked in close collaboration with Dr. R. G. Snyder, efforts to classify cases of chronic arthritis seen in office practice, solely on the basis of roentgenologic findings, have often met with failure. It seems that in the final analysis the clinician must still, in most instances, rely on his clinical judgment for the etiologic classification of chronic arthritis. It follows, therefore, that in a case of chronic arthritis which seems to belong to one of the three groups, known as atrophic (rheumatoid), hypertrophic (osteo-arthritic), or mixed, the clinician still must rely largely on his clinical judgment in deciding whether the discovery and eradication of foci of infection, toxemia or allergic irritation will be of clinical value in the management of the case.

#### ROENTGENOLOGIC AID IN THE STUDY OF THE ARTHRITIDES

The roentgenologist can be of great assistance to the clinician in the search for obscure foci or obscure causes of joint pain. Careful study of the teeth, paranasal sinuses, lungs, heart, gallbladder, kidneys, gastro-intestinal tract and skeletal structures may disclose foci of important etiologic relationship to the arthritic process. Roentgenologic study may bring to light abnormalities of posture, bony anomalies, soft tissue pathologic processes, pathologic processes in the organs and skeletal structures, which may immediately clarify many obscure cases of joint pain and aid materially in establishing the diagnosis.

In postural arthritis (static, endogenous, traumatic) the demonstration of flattening of the arches of the feet may explain painful ankle or knee joints and pains in the hips and lower back.

Scoliosis or abnormal lordosis, kyphotic arching of a spine segment, malalignment of the various segments of the spine in their relationship to each other or to the sacrum, may elucidate obscure cases of neck pain, backache, and pain in the chest.

Anomalies of the spine, such as congenital malformation of the articulations, dehiscence in the posterior arches of the vertebral or sacral segments and sacralization and malarticulation of the lowest lumbar vertebrae may explain the cause of painful symptoms in these regions.

In rare cases the disclosure of an old intracapsular fracture with subsequent development of bony spurs or atrophic changes and narrowing of the joint space may disclose the reason for joint discomfort.

The roentgenologic demonstration of a psoas abscess, long before there are roentgenologically demonstrable vertebral changes (Ornstein and Ulmar<sup>35</sup>), may aid in discovering an early tuberculous arthritis of the spine.

Paget's disease of the shoulder, knee and hip or of the spine and pelvis has on many occasions been treated as "rheumatism" before roentgenologic examination disclosed the true condition.

The joint complaints of the acromegalic patient may be clarified by the demonstration of the sella and skull changes, namely, enlargement of the sella, with or without atrophy, general enlargement with sclerotic changes of the skull, facial bones, lower jaw and the increased size of the extremities, particularly hands and feet.

The joint symptoms of the hyperparathyroid case, with collapse at times of some of the vertebral bodies, become clear when the generalized bony rarefactive changes and bone cysts are found. The mottled rarefaction of the skull and of the facial bones and the demonstration of urinary calculi may be the first clue leading to the demonstration of the characteristic chemical findings of hyperparathyroidism.

In large tumor clinics it is not at all uncommon to find cases which had been treated for months for a supposed arthritis

which on roentgenologic examination show the characteristic evidence of a local neoplasm, benign or malignant, or the destructive changes of bone metastases.

# SEARCH FOR FOCI IN ATROPHIC (RHEUMATOID), HYPERTROPHIC (OSTEO-ARTHRITIC), AND MIXED FORMS OF ARTHRITIS

**Teeth.**—Roëntgenographic examination of the teeth and surrounding structures may reveal the following:

1. Localized marginal pericementitis around vital teeth, due to pocket formation under overhanging metal fillings, food débris accumulations, alveolar recession, and dental caries.
2. Generalized pyorrhea, with extensive recession and absorption of the alveolar margin and formation of pockets around vital teeth, which may discharge pus and extend completely around one or more teeth.
3. Hypercementosis of dental roots, due to marginal pericementitis, or to low-grade infection with chronic irritation of the pulp.
4. Unerupted or partially erupted teeth with decay and infected pocketing.
5. Malposed teeth with decay, alveolar septic pockets, or even fairly extensive destructive changes of the alveolar bone.
6. Either nonvital or devitalized teeth with pericemental thickening or early granulomatous apical changes.
7. Incomplete or imperfect filling of root canals with pericementitis or granuloma.
8. Drilled false root canals with pericementitis or abscess formation.
9. Extensive caries, usually under metal fillings, which has extended to the pulp chamber and probably has caused the death of the tooth.
10. Apical pericementitis, where very large metal fillings resulted in the death of the tooth pulp. In these cases one sees thickening of the pericementum at the apex, associated often with hypercementosis of the roots. The hypercementosis represents the response of the tooth to a chronic low-grade infectious process in the pulp.
11. Apical granuloma, a more advanced stage of apical pericementitis. In granuloma the pericementum becomes detached from the root apex.
12. Apical epithelial cyst (radicular cyst), which represents a still later stage of dental root infection, in which the central portion of the granulomatous mass becomes liquefied. One must bear in mind that granuloma and apical cysts may be separated from the antrum by an extremely thin plate of bone, or may point directly into the antral cavity where the bony floor is dehiscant and may be separated from the antral cavity only by antral mucosa. An infected dental cyst may break into and infect the maxillary sinus and possibly by continuity, the other nasal sinuses.
13. Chronic root abscess with destruction of the pericementum, possible partial absorption of dental roots and bone scar formation in the alveolar structure surrounding the root. Chronic root abscesses may invaginate and infect the maxillary sinuses.

14. Diffuse alveolar bone destruction, starting immediately around the infected nonvital tooth and extending well into the surrounding alveolar structure.
15. Root fragments with a walled-off infective process or with an apical epithelial cyst.
16. Root fragments pushed into the antrum during extraction. These are usually associated with a draining oral fistula and infection of the antrum.
17. Maxillary fistula into the oral cavity at the site of dental extraction. If infection of the antrum follows and is not properly managed, a draining fistula with infection of the antrum and socket may persist for years.
18. Infected root cyst, left in alveolus after dental extraction.
19. Infected socket partially or completely closed over by alveolar healing before thorough drainage of infected material had taken place.
20. Socket infection associated with a diffuse low-grade osteomyelitic process of the adjacent bone.

The possibilities of dental infection are indicated here in detail to show the great care with which dental roentgenograms must be studied for their proper evaluation. The writer has repeatedly observed cases in which clinicians were satisfied to rule out dental infection on the basis of improperly made roentgenograms on which, at best, only the very gross and obvious pathologic changes could have been visualized. Not infrequently clinicians err in requesting incomplete dental examinations, limited to the remaining teeth only. In such cases it is not unusual to overlook completely the presence of infected root fragments, cysts, septic pockets, antral fistulas or low-grade osteomyelitis of the alveolus.

It should be evident from the above discussion that radiologic examination of the teeth and alveoli merits extremely careful study, if dental and alveolar infection is to be ruled out on the basis of such study.

**Paranasal Sinuses.**—The paranasal sinuses are often disregarded as an etiologic factor in chronic arthritis because of lack of clinical history of sinus involvement. It must be remembered, however, that marked pathologic changes may occur in the sinus membranes and cavities, with but very slight or no local subjective symptoms.

The rule should be to examine the paranasal sinuses of every arthritic patient in whom a focus is suspected, regardless of lack of history of sinus involvement (Hurd,<sup>30</sup> 1933).

Rhinologic examination may fail entirely in disclosing existing sinus pathology. This is particularly true where the posterior groups of sinuses are involved.

Roentgen examination of the sinuses may fail to disclose disease if great care is not taken with the many technical details essential in the production of good roentgenograms. The permissible latitude of technical error in the quality of sinus roentgenograms is very slight. The diagnostic value of sinus roentgenograms may be lost completely through faulty technic. In complicated and postoperative cases, many views at different angles may be required for proper visualization of the various sinus cavities. Views with the head inclined to one side may be necessary for the demonstration of fluid levels in the maxillary sinuses. For study of the frontals and ethmoids the orthodox postero-anterior and lateral views may have to be supplemented by oblique views of each side. For better visualization of disease processes along the antral floors particularly where sinus disease originates from dental structures and alveoli, the usual antral views may have to be supplemented by views taken obliquely between the rami of the mandible or by exposures made from behind, centering the rays through the space between the mandible and cervical spine. In some cases additional postero-anterior views may be necessary, exposed at such angles that the occipital rim and petrous bones will not overshadow the antral floors. Study of the sphenoids requires views that must show the right and left sphenoids separately. It may be necessary at times to make additional exposures, projecting the sphenoids on films placed in the mouth or utilizing angles which will project the sphenoid roofs into the frontal sinus area.

In chronic cases, particularly in postoperative cases, the routine roentgenograms may not suffice and some views may have to be repeated with deliberate overpenetration of the skull structures, in order to bring out some detail obscured by chronic hyperplastic or fibrotic changes. At times all these views may have to be supplemented by study of roentgenograms made after injection of opaque materials into the sinuses.

Slight movement of the head during roentgenographic exposure may completely ruin diagnostic detail. Slight rotation of the head on its vertical axis may produce false shadows which may lead to erroneous interpretation. The use of roentgen rays which are slightly overpenetrating or underpenetrating for the particular texture and calcium content of the skull

under examination, may completely blot out informative detail on the roentgenograms. The use of developing chemicals which are old, or at a higher or lower temperature than normal may completely nullify the diagnostic value of the roentgenograms.

In sinus roentgenography it is essential to expose and develop each film or stereoscopic set of films as the roentgenologic examination proceeds so that errors of technic may be rectified immediately.

Stereoscopic views are exceedingly helpful, and in many cases indispensable. The proper evaluation of sinus roentgenograms requires, as a minimum, views taken in four different positions, a lateral view, two postero-anterior views at different angles for the ethmoids and antra, and a cephalocaudal view for demonstration of the sphenoids. In addition to these the other views above described are often very necessary for the study and proper interpretation of sinus roentgenograms.

There is another reason why the sinuses are often overlooked as an etiologic factor in chronic arthritis, and that is the failure to regard roentgen evidence of thickened and polypoid membrane as indicative of possible sinus infection. There is a common tendency to disregard all roentgenologic findings in the sinuses if free pus cannot be demonstrated. It must be remembered, however, that thickened and polypoid membrane may in itself harbor infection, or may cover up abscess pockets.

### LUNGS AND HEART

In the investigation of the lungs roentgenologic examination is limited largely to the demonstration of chronic empyema, abscess, diffuse pulmonary suppuration and bronchiectasis. Cardiac infections present very little definite roentgenologic evidence. Nevertheless, studies of the heart contours and action are of value to the clinician in determining the presence of infective cardiac lesions.

### GASTRO-INTESTINAL TRACT

In the gastro-intestinal tract study of the colon may yield information of great value. In the esophagus, stomach and duodenum, if symptoms referable to these organs are



present, roentgenologic study may reveal diffuse inflammatory changes or localized ulcerations which may be of etiologic significance.

In the colon several conditions must be looked for. The most important is evidence of colonic stasis. Examination of the colon by barium enema, without preparatory cleansing of the bowel is the method of choice for the demonstration of colonic stasis. The colon should be examined routinely in all cases of chronic arthritis, regardless of history of normal bowel habits. It is surprising how frequently evidence of stasis or of colonic infection can be found in patients whose history does not point to bowel disturbance. It is not at all unusual to find the entire colon packed with fecal masses even shortly after bowel evacuation. In some cases, one finds localized spasm and serration and occasionally even partial obstruction at the site of colonic diverticula in the sigmoid or descending portion of the colon, indicating the presence of infected diverticula. In other cases, one may find abnormal dilatations of the colon due to gas accumulation or fecal stasis or very marked redundancy with kinking or looping of the bowel segments. In some cases the evidence of bowel irritability, namely marked spasticity, is further strengthened by the finding of marked turgescence and increase in the arborization of the mucosal folds, indicating the probable presence of catarrhal colitis. Occasionally ulcerative colitis may be demonstrated in arthritis patients.

The roentgenologic demonstration of irritability, stasis or infection of the gastro-intestinal tract is of great value to the clinician. There is fairly general acceptance today of the theory that such factors are of etiologic importance in chronic arthritis and must be eliminated if possible for the successful management of the case.

#### APPENDIX

Chronic appendicitis is a condition which does not lend itself readily to roentgenologic investigation. The roentgenologist can visualize the appendix, in most instances, if the appendiceal lumen is not obliterated. He can demonstrate the mobility of the appendix or its retrocecal position or unduly long retention of the opaque medium. He can elicit localized

tenderness by pressure directly over the appendix. The clinician must then evaluate these findings in the light of his clinical findings and laboratory data.

### GALLBLADDER AND URINARY TRACT

The search for gallbladder and urinary tract infection lends itself readily to roentgenologic investigation. The demonstration of enlarged, thickened, calcified gallbladders, of gallbladder adhesions, of gallstones, of pathologic conditions of the gallbladder, mucosa and of the urinary tract by modern roentgenologic methods is a comparatively fruitful field for roentgenologic investigation.

### BONE INFECTION

Old osteomyelitic infections of the bony skeleton and chronic mastoid infections are readily demonstrable roentgenologically.

From the above enumeration of roentgen studies of the teeth, sinuses, heart and lungs, gastro-intestinal tract, urinary tract, gallbladder and skeletal structures, it is evident that the roentgenologist can be of considerable assistance to the clinician in the search for obscure foci in chronic arthritis.

### ROENTGEN RAY THERAPY OF CHRONIC ARTHRITIS

A number of favorable reports have appeared in the literature on the use of roentgen ray therapy in chronic arthritis.

Scott<sup>37</sup> advises small doses of low penetration, and uses rays of comparatively high penetration in his hip cases. He obtained good results in "infective" and hypertrophic arthritis, but not in the atrophic cases.

Kahlmeter<sup>38</sup> reports that x-ray radiation is valuable in both the atrophic (rheumatoid) and hypertrophic (osteo-arthritic) forms of arthritis. He uses small fractionated doses at two- to three-day intervals. Sixty per cent of the atrophic cases and 40 per cent of the hypertrophic cases were benefited by this form of treatment. His atrophic spondylitis cases, however, failed to respond. He thinks the beneficial effect is due to reduction of capsular swelling and diminution of joint exudate. The analgesic effect may become evident within two or three days or not until two or three weeks after commencement

of treatment. Improvement may last for months. Certain patients responded to this form of therapy in whom all other methods had failed.

Douthwaite<sup>39</sup> (1932) is less optimistic as to the value of "deep x-ray therapy" in hypertrophic arthritis (osteo-arthritis). He feels that anything in the nature of a lasting improvement occurs in the minority of patients. The relief of pain, however, justifies the trial. He warns, however, against overdosage with its danger of leukopenia.

Watt<sup>40</sup> (1933) obtained 40 per cent of cures and marked improvement in 194 cases of hypertrophic arthritis (osteo-arthritis). The joints treated were the knees, hands, shoulders, hips and lumbar vertebrae (remaining joints rarely). He used from 50 to 60 per cent of a skin erythema dose, spread over 2 to 4 sittings and repeated in from six to eight weeks, when necessary. In the hypertrophic type, radiation is the treatment of choice and should be given early. In cases of long standing with disappearance of cartilage, deformity and bony overgrowth, the most one can hope for is relief of pain and some lessening of disability.

Hernaman-Johnson<sup>41</sup> (1931) thinks that x-ray radiation is least effective in atrophic (rheumatoid) arthritis. He obtained the most striking results in hypertrophic arthritis (osteo-arthritis). He believes the effect is due to the analgesic effect of the treatment, to reduction of joint congestion and to absorption of pathologic fibrous tissue.

Fried<sup>42</sup> (1934) states that roentgen treatment has at least two very desirable effects, namely, a rapid analgesic result and a decrease of swelling. These effects are similar in acute, sub-acute or the chronic stages in the infective, rheumatic or deforming types of arthritis.

Langer<sup>43</sup> (1933) claims that the majority of patients are benefited but that the results may not be apparent in some cases for several months.

#### SUMMARY

1. The chronic arthritides can be divided clinically into 9 main groups.
2. Roentgen classification of chronic arthritis on an etiologic basis is subject to many errors.

3. Roentgenologists today are generally of the opinion that the chronic arthritides of specific infectious origin do not present sufficient pathognomonic roentgen evidence to indicate the etiologic factor in each type. The roentgen changes may be of the atrophic, hypertrophic or mixed variety depending on the duration of the disease, the age of the patient and individual response of the patient to his infection.

4. Similarly the joint changes of the neuropathic arthritides and of those caused by faulty endocrine, metabolic or chemical processes and trauma are not sufficiently pathognomonic for an etiologic roentgen diagnosis.

5. In typical cases the roentgen appearance is sufficiently characteristic for a tentative roentgenologic diagnosis of atrophy (rheumatoid) or hypertrophic arthritis (osteo-arthritis). In many instances, however, the roentgenologist may find great difficulty in differentiating between these two forms of chronic arthritis. Roentgen evidence of both types may be present in the same patient and even in the same joint. Either type may predominate and largely mask the other. The final diagnosis should be made after consultation with the clinician and the correlation of all known facts.

6. The roentgenologist can be of considerable aid to the clinician in the discovery of obscure foci.

7. Roentgen demonstration of foci is dependent often on meticulous attention to numerous technical details of roentgenography.

8. Roentgen therapy of certain types of chronic arthritides may be of considerable benefit.

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## CLINIC OF DR. MARTIN HENRY DAWSON

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### THE RÔLE OF THE STREPTOCOCCUS IN CHRONIC ARTHRITIS<sup>1</sup>

THE subject originally assigned for this clinic was "The Rôle of the Streptococcus in Chronic Arthritis." This vague title is no longer acceptable, for chronic arthritis cannot be regarded as a single disease entity. It includes a multiplicity of clinical conditions, many of which have nothing to do with infection in any way: for example, gout, trauma and neurotrophic disturbances. So, also, there are many varieties of chronic arthritis associated with specific infections, such as tuberculosis, gonorrhea, lymphogranuloma inguinale and many others. It is obvious that streptococcal infection plays no rôle in the pathogenesis of such conditions.

There remain, however, two great groups of chronic arthritis in which the rôle played by streptococcal infection has been debated for many years. These two varieties are variously designated by the following terms:

1. Osteo-arthritis, hypertrophic or degenerative arthritis.
2. Rheumatoid, atrophic or chronic infectious arthritis.

It is now generally accepted that these two forms constitute separate and distinct disease entities. Furthermore, it is being increasingly recognized that osteo-arthritis or hypertrophic arthritis is an age-period, degenerative disease and that infection plays no rôle in its pathogenesis. The precise cause of this form of arthritis is not known, but it is believed that constitutional tissue inferiority and trauma are important etiologic factors.

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Thus, there remains to be considered only one group, rheumatoid, atrophic or chronic infectious arthritis. Since the early days of bacteriology, this form of arthritis has generally been associated with some form of infection and much emphasis has been placed on the rôle played by streptococcal infection.

Rheumatoid arthritis is a systemic disease of unknown etiology, characterized by a chronic and progressive involvement of the articular structures. Although the disease picture is classical in its typical form, it may present the widest variations in individual cases. In spite of its protean manifestations, however, it exhibits certain clinical characteristics which justify the belief that it constitutes a single clinical entity. There now seems no justification for a separation of cases into such categories as "infectious" and "atrophic." Furthermore, several clinical entities heretofore regarded as separate diseases are now believed to be varieties of rheumatoid arthritis. Among these are rheumatoid spondylitis (Marie-Strümpell), Still's disease and psoriasis arthropathica. Such conditions are included in the present discussion.

Before proceeding to a detailed discussion of the evidence for and against streptococcal infection in rheumatoid arthritis, it is first necessary to consider some of the newer bacteriologic knowledge concerning the streptococci themselves. In general, streptococci are of three main varieties: the hemolytic, the green-producing or viridans and the indifferent. The hemolytic streptococci constitute by far the most important of these varieties and because of their overwhelming importance they have become the subject of intensive research by many investigators. Lancefield has shown that distinct groups exist within the hemolytic variety itself and that practically all strains which are pathogenic for man belong in Group A. Strains belonging to the other groups are frequently found as harmless saprophytes in man, but only in occasional instances are they responsible for clinical infection. For example, one of the natural habitats of Group D strains is the gastro-intestinal tract, but there is no evidence that these strains are ever pathogenic. Hare has shown that only about one third of the strains of hemolytic streptococci found in the upper respiratory tract of normal human beings belong to Group A. The remaining strains belong to groups which are essentially non-



pathogenic. These findings are of the utmost significance in the consideration of any disease thought to be associated with streptococcal infection.

Another fact of great importance in the newer knowledge of hemolytic streptococci is that a large number of distinct types exist within each group. Griffith has demonstrated at least 24 separate serologic types within Group A alone and probably others exist. As a result of these findings, it is now possible to determine not only the group to which each individual strain belongs, but also the specific type within that group.

The green-producing and the indifferent streptococci are among the most ubiquitous of all bacteria. They are widely distributed in nature and in man, but only in occasional instances are they ever pathogenic. Except in conditions such as subacute bacterial endocarditis, their rôle is almost exclusively confined to that of secondary invaders.

#### IMMUNOLOGIC TESTS FOR STREPTOCOCCAL INFECTION

Because of the wide importance of streptococci, particularly those of the hemolytic variety, a large number of immunologic tests have been devised to determine the presence of streptococcal infection. The more important of these are the following:

(a) **Agglutination Reactions.**—It is a well-known fact that agglutination reactions with streptococci are attended by great technical difficulties. Even in diseases definitely known to be associated with streptococcal infection, such as scarlet fever and erysipelas, conclusive results are difficult to obtain. In diseases of more uncertain etiology the results must be clearly defined before they can be considered as significant.

(b) **Precipitin Reactions.**—A number of precipitin reactions have been devised for the study of hemolytic streptococci under experimental conditions. The tests can only be carried out by experienced investigators and even in their hands the reactions do not yield information of any clinical value.

(c) **Complement Fixation Reactions.**—Complement fixation reactions can be obtained in a number of streptococcal diseases, but the results tend to be nonspecific in character.

Some of this difficulty is due to the fact that the various antigens employed contain nonspecific fractions which are common to a variety of related organisms. In general it may be stated that up to the present time no complement fixation reaction has been devised which specifically establishes the presence of streptococcal infection.

(d) **Antistreptolysin.**—Todd has recently shown that the hemolysin of hemolytic streptococci is antigenic and that, following acute hemolytic streptococcal infections, there is a marked increase in the antistreptolysin titer of the patient's serum. This test is of value in determining the presence of recent, acute, hemolytic streptococcal infection, but it is of little or no assistance in demonstrating the presence of low-grade or chronic infection.

(e) **Antifibrinolysin.**—Tillett has shown that, following acute hemolytic streptococcal infection, the serum acquires antifibrinolytic properties. Like the antistreptolysin test this reaction is of value in demonstrating the presence of recent acute infection, but it is of no value in determining the presence of low-grade, chronic infection.

(f) **Skin Tests.**—Skin tests done with streptococcal vaccines and extracts have been widely used by many investigators in attempts to demonstrate the presence of streptococcal infection. For the most part this type of work has been uncritical and lacking in adequate controls. After a detailed study of the problem Short, Dienes and Bauer concluded that without using several subjects as controls skin tests are without significance. Even with such precautions these workers state that skin tests are of no value in selecting strains suitable for vaccine therapy. In all work of this nature it must be constantly kept in mind that the skin sensitivity of a patient does not *prove* the existence of any relationship between the disease and the material that produces the skin reaction. It may suggest that the particular individual is either infected with, or is a carrier of, the organism in question, but it does not establish the fact that the symptoms of the disease are in any way related to the degree of sensitivity present.

From the foregoing résumé it is apparent that present immunologic and serologic methods are inadequate to establish the presence or absence of streptococcal infection. Although a

large number of tests are available, in the aggregate they can only yield evidence which at best is suggestive in nature.

#### EVIDENCE FOR STREPTOCOCCAL INFECTION IN RHEUMATOID ARTHRITIS

(A) **Direct Bacteriologic Evidence.**—1. *Cultures from the Blood and Tissues.*—Since the earliest days of bacteriology innumerable investigators have claimed to have isolated various forms of bacteria from the blood and tissues of patients suffering from rheumatoid arthritis. Some form of streptococcus seems to have been most frequently encountered, but there has been the widest divergence in the type of streptococcus recovered. Many investigators have consistently obtained negative cultures while others have obtained a variety of organisms. The complete lack of agreement in the results would in itself seem sufficient reason for regarding the findings with grave suspicion. It must be concluded that up to the present time no convincing evidence has been brought forward that streptococci are actually present in either the blood or tissues of patients suffering from this disease.

2. *Cultures from So-called "Foci of Infection."*—The failure to demonstrate bacteria in the blood and tissues has led to a large amount of investigation on the bacteria found in so-called "foci of infection." Here again some form of streptococcus has been frequently encountered, but there has been the same wide diversity in the nature of the strains. In all such investigations it must constantly be kept in mind that streptococci are almost ubiquitous in their distribution and that the finding of such organisms in the upper respiratory tract, the gastro-intestinal tract and on the skin is entirely without significance. All tonsils harbor streptococci within their crypts and in a recent study at the Presbyterian Hospital it was shown that over 90 per cent of enucleated tonsils contained streptococci of the hemolytic variety. Mention has already been made of the fact that the gastro-intestinal tract is a natural habitat of one of the groups of hemolytic streptococci. From the studies reported to date it appears that streptococci are not found any more frequently in arthritic patients than in normal individuals or in patients suffering from other diseases.

3. *Reproduction of the Disease in Animals by the Injection of Streptococci.*—Loeffler in 1886 was one of the first to pro-

duce arthritis in animals by the injection of streptococci. Since his time a large number of investigators have repeated this work but no one has yet succeeded in reproducing the true disease, rheumatoid arthritis. It is a comparatively simple matter to produce a low-grade septic arthritis in rabbits by the injection of streptococci of low virulence, but the disease so produced differs in certain essential respects from the naturally occurring disease. There is no evidence whatever that strains of streptococci recovered from patients suffering from rheumatoid arthritis are more effective in causing arthritis in animals than strains obtained from other sources and an entirely similar form of arthritis can be produced by many bacteria other than streptococci. It must therefore be concluded that such experiments contribute little or no evidence in support of the streptococcal theory of the etiology of rheumatoid arthritis.

**(B) Indirect Evidence of Streptococcal Infection.**—1. *Clinical History of the Disease.*—This constitutes one of the most cogent arguments in support of the streptococcal theory. It is generally acknowledged that in a significant proportion of cases the disease appears to be initiated by streptococcal infection. In our experience a definite history of such infection can be obtained in from 20 to 25 per cent of cases and invariably the streptococcus is of the hemolytic variety. In a further 20 to 25 per cent of cases a more equivocal history can be obtained. On the other hand, a large number of cases are encountered in which absolutely no history or signs of such infection can be elicited. In such cases the possibility of latent infection must be considered, but at the present time no methods are available to determine the significance of infections of this nature. In general it may be stated that the evidence obtained from clinical histories, while suggestive, is far from conclusive in establishing the rôle played by streptococcal infection.

2. *Immunologic Tests.*—(a) *Agglutination Reactions.*—In recent years a large amount of work has been done on agglutination reactions in rheumatoid arthritis. It has been established that in the majority of cases the sera of patients agglutinate hemolytic streptococci belonging to Group A in significantly high dilutions. However, great care must be exercised in interpreting these reactions. In the first place, it is

well known that agglutination reactions with streptococci are technically difficult to perform and cannot be done as a routine procedure. Experience has shown that the *strength* of the reaction is of greater significance than the actual *titer*. In the second place, although the reactions are highly characteristic for Group A hemolytic streptococci, the possibility remains that they may be nonspecific in nature. Finally, it must be kept in mind that even if streptococcal infection is present it may play a rôle of secondary rather than of primary importance.

(b) *Precipitins*.—Precipitin reactions with fractions of hemolytic streptococci suggest the presence of infection with Group A hemolytic streptococci in some cases of rheumatoid arthritis. From the practical point of view the tests are of no value in routine examinations.

(c) *Complement Fixation Reactions*.—Among the chief exponents of complement fixation reactions in arthritis are Burbank and Hadjopoulos. However, these workers themselves state: "The test is not diagnostic for arthritis alone but is diagnostic of a wide group of acute and and chronic infections that give rise to antistreptococcic bodies in human serum." The results of Burbank and Hadjopoulos can be further criticized because of their use of raw or unheated serum in fixation tests. It has long been known that active sera frequently fix complement nonspecifically and their use has been generally abandoned by workers in this field.

(d) *Antistreptolysin and Antifibrinolysin*.—These reactions have been studied by a number of workers in rheumatoid arthritis with rather equivocal findings. In the majority of chronic cases the results are within normal limits, but in many early and acute cases definitely high values are obtained. The findings suggest that in certain cases the disease is initiated by hemolytic streptococcal infection, but there is no evidence that the activity or persistence of the process is associated with the continuance of such infection.

(e) *Skin Tests*.—From the comments already made on the futility of skin tests in determining the presence of streptococcal infections in general, it would be expected that such tests would have little or no value in rheumatoid arthritis. Such indeed is the case. The skin reactivity of arthritis patients has been investigated by many observers and the results appear to be quite without significance.

*Allergy.*—Because of the failure to demonstrate bacteria in the tissues, numerous investigators have had recourse to the theory of bacterial allergy in its various forms. A detailed discussion of the evidence for and against this concept is not possible within the limits of this clinic. However, it can be stated that at present allergy is little more than an hypothesis and a rather unsatisfactory one at that. Profound as is our ignorance concerning the etiology of rheumatoid arthritis, many observers prefer to admit that ignorance rather than to accept an unproved theory which may only lead to further false assumptions and conclusions. In particular the hypothesis of allergy has led to a number of therapeutic procedures designed to "desensitize" the joints and tissues. Experience tends to cast much doubt on the value of all such procedures and an increasing number of clinicians are abandoning their use.

#### SUMMARY

The evidence so far available does not permit the formulation of any final opinion concerning the rôle of streptococcal infection in rheumatoid arthritis. Such evidence as there is incriminates streptococci of the hemolytic variety. There is no evidence that viridans or indifferent streptococci are concerned in the pathogenesis of this disease.

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## CLINIC OF DR. CLARENCE A. DUNN

### ROOSEVELT HOSPITAL AND HOSPITAL FOR THE RUPTURED AND CRIPPLED

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#### ORAL FOCI IN ARTHRITIS

ANY discussion of arthritis would be incomplete without the consideration of mouth infection. At one time no attention was given to mouth infection, and unquestionably many cases of arthritis were pronounced as incurable, and the patient doomed to many years of suffering, where the elimination of some focus in or around the teeth and jaws would have brought great benefit to the sufferer.

With the theory of focal infection came the period of the wholesale, and often entirely unnecessary, removal of all the teeth, with no apparent benefits in the systemic disease, and the unfortunate one was rendered a dental cripple for the rest of his life. Fortunately, with the advent of  $x$ -ray, this condition has largely been corrected, though an opinion should never be accepted upon the  $x$ -ray findings alone, for many times foci that do not show by  $x$ -ray can only be uncovered by careful clinical examination. At the present time the pendulum is swinging from the wholesale removal of teeth to a saner and more conservative viewpoint. Close cooperation between the dental and medical professions is to be desired to prevent irreparable damage being done to the patient from both a medical and dental standpoint.

Since the advent of the theory of focal infection has been proved, much has been written concerning the rôle of pulpless teeth in systemic disease, and no hard and fast rule can yet be stated concerning them. Before the use of the  $x$ -ray it was common practice to pass these teeth as healthy, but radiographic examination proved many of them to be a menace.

Obviously, all pulp should be removed. arthritic condition, that some other foci that it is only in indirect rôle, but any is a menace to the get removed. It is in those evidence of pathology retention becomes a pre majority of this class of after the elimination of official results, then the re indicated.

Pulpless teeth are by no for as a focus in the mouth with their attending infectio alveolar process, gingivitis, bridge work, and Vincent's i: foci as are pulpless teeth.

Any infection in the mouth of the body by direct absorpt. absorbed through the gastro-inte sity of proper treatment of oral c radiographic examination.

Impacted teeth should be ren crown has erupted through the alv made no provision for the attach crown of a tooth, so consequently, erupted, an ideal point of entrance fo produced. Cultures taken from pool partially erupted teeth invariably give

Pyorrhea must always be eliminat health can be given on the mouth. To produced by this condition are unque and pressure of the gums around them of pus. If the disease has progressed to alveolar process has been absorbed so r loosening of the teeth, has gained access of the roots of the multirooted teeth, or



proper treatment, then the only safe procedure is the removal of the affected teeth.

It is important that complete x-rays be taken of every mouth, regardless of how long the teeth may have been removed, for in a large percentage of edentulous mouths will be found root fragments or residual infection.

The removal of oral foci, while not a panacea in the treatment of arthritis, is certainly important, and in certain cases will be found to be the direct cause of the disease. If not the direct cause, the elimination of the oral foci is to be desired, for it will unquestionably improve the general health.



## CLINIC OF DR. PAUL H. BREUNING

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#### THE TONSILS AS FOCI OF INFECTION IN ARTHRITIS

INFECTION within the tonsils and pharyngeal lymphoid tissue has long been recognized as associated with acute and chronic arthritic symptoms. In any given case there is likely to be considerable controversy among the attending clinicians as to whether the tonsils are acting as a focus of infection or as the source of toxic irritation to the joints. Recently an effort has been made to emphasize that they are only of etiologic importance in rheumatoid arthritis and that they are only coincidentally infected in cases of osteo-arthritis. On the other hand, many experienced clinicians feel that they may act as direct etiologic factors in both types of arthritis. These differences of opinion emphasize the fact that tonsillar clinical diagnosis has not yet been perfected.

The anatomy is well known to all, but the physiology is more vague. We are accepting the premise that the tonsils in health are a destroyer of local infection and a guardian against the entrance of this infection into the general system, especially during the period of the exanthematous fevers of childhood. This is probably the period which largely controls the rest of the life of the tonsils. The throat being the site of attack common to most all childhood contagions and infections, it is not surprising that by the age of puberty considerable damage may have been done to the cellular structures of the tonsils, with consequent hypertrophy and formation of scar tissue. If the tonsil has withstood these attacks upon it during this period and has been able to carry on its functions with efficiency, it probably will follow its natural course, gradually atrophying, until later in life it becomes so small and flat that the tonsillar fossa will appear practically empty.

Our problem is to determine what diagnostic signs are present that lead us to believe that the tonsil is acting as a focus of infection, and whether this toxic influence is affecting distant organs, such as the joints, in any given case of arthritis. These clinical signs are to be carried in mind during the examination of every case. Moreover a complete tabulation should be made of distinctive features in order that the examiner may have an exact picture of the tonsil as it appeared at the examination so that later the picture of the tonsil may be accurately recalled when checking up the present status of the patient.

The factors upon which conclusions are based and opinions made vary so greatly that absolute diagnosis can only be made in a moderate percentage of cases. But the conscientious correlation of these factors will enable one to give a very helpful opinion in a large percentage of cases, and in a definite, though perhaps small, percentage absolute answers instead of opinions can be given from the clinical signs and history.

The aim of this article is first to state for the general practitioner and the specialist in other branches of medicine, the principles of tonsillar diagnosis, and secondly to show that infected tonsils are found in the great majority of cases of rheumatoid arthritis. Thirdly we wish to emphasize that infected tonsils are also found in cases of osteo-arthritis and that even in these cases their removal is frequently followed by a satisfactory improvement in the patient's symptoms, provided all the other possible etiologic factors are also eliminated.

Quite significant is any difference noted in the appearance of the two tonsils. Since they are both influenced by the same physiologic conditions, a breakdown in normal function of one may be quickly demonstrated by comparing it with the other. Other features to be carefully recorded are:

1. Size.
2. Embedded or coverage by pillars.
3. Consistency, sclerotic and hard or soft and spongy.
4. Color, pale or congestively red.
5. Circumtonsillar flush, caused by congestion of mucous membrane of anterior pillar and soft palate; its depth of color and width are very significant as to the amount of irritation underneath
6. Determination of contents of crypts by pressure against anterior pillar behind the tonsil, with a blunt or a hard retractor, partially evulsing gland,

will usually express its contents where there are large deep clefts or crypts: if no acute inflammation is present, blowing air down into them through a cannula or straightened eustachian catheter may be used to force contents out, or suction through a wide-mouthed glass tube, fitted over the tonsil, will bring out its foreign contents.

7. Characteristics of substance expressed, chalky concretion, caseous, creamy, milky and if odoriferous, bacterial examinations of this material will help, especially with the repeated finding of a vicious hemolytic organism in the expressed substance from the gland.

8. The presence of an enlargement of the lymphatic glands of the neck, particularly under the angle of the jaw.

Upon the sum of these findings and the review of the history, such as a relation between acute throat flare-ups and distant systemic symptoms, you will have the material for judging the guilt of the tonsils and whether capital punishment is to be invoked.

We will classify the various infected tonsils under acute, subacute and chronically infected tonsils.

The acute infection picture is a familiar one. The tonsils are usually red or angry looking, and more or less swollen, and with or without exudate and minute abscesses in the tonsillar crypts. There is usually red congested mucous membrane throughout the throat, accompanied by general toxic symptoms. While this condition is present or subsiding, if joint symptoms commence or there is an acute exacerbation of a chronic arthritic condition, we have a logical link, with its sequence almost becoming obvious. If there is a previous history of this same sequence having occurred before, there can be little doubt as to at least one of the factors contributing to the joint derangement; and removal of the tonsils will bring gratifying results and help greatly to reduce the probability of slowly developing joint changes, which are most likely eventually to follow. Even though the condition clears up entirely in the joints, following the resolution of the throat lymphatic structures, the tonsils should be removed as a prophylactic measure. Where the above close sequence between the acute tonsillar infection and the appearance of arthritic symptoms has been present in the history, the writer has noticed a more frequent, temporarily acute exacerbation of arthritic symptoms arising following the subsequent tonsillec-

tomy, than where no such sequence was noted in the previous history.

Our greatest difficulty arises in expressing our opinion where the subacute and chronic tonsils are in question, as these two conditions blend one into the other, and the diagnostic signs in relation to arthritis apply to each. They will be treated here together.

The type of tonsil, simulating most of the subacute infected gland but in reality a chronic infection, is the very large, dull red, spongy tonsil, from which little if any secretion can be expressed. The band of congestion, along the anterior pillars and the soft palate, is wide and deep in color, if other signs of acute throat inflammation are lacking. The tonsils are protruding and tend toward being obstructive. There is usually some enlargement of the lymphatics at the angle of the jaw or of the cervical chain, but as they are usually found in fat, thick-necked type of persons, it may be difficult to feel these glandular enlargements. The patient having this type of tonsil is usually surprised to hear his tonsils are bad, and will state he has never had any throat trouble in his life. This type of tonsil is seen very frequently in clinics where there are many southern Europeans. Where these conditions are found, the tonsils can practically always be considered as an infective focus and will require removal.

A difficult tonsil to judge is the small, hard, pale gland, which appears normal at first. The size may not be due to atrophy but to a fibrosis, resulting from long-standing, inflammatory irritation, and be largely covered by the anterior pillar, due to adhesions. The outer layer is sclerotic and together with the pillars drawn over tightly; the glandular tissue becomes enclosed. If there is infection within, which there usually will be with these conditions present, some of the before-mentioned clinical signs will be present. The most frequent and indicating sign will be a heavy band of circumtonsillar congestion and will indicate that there is marked irritation within. Because of the necessity for absorption of the resulting products from such a deeply placed infection, there will be a prominence of the gland at the angle of the jaw or of the cervical lymphatic chain, and usually an increased sensitiveness of the tonsil or pressure behind it. This type of small

tonsil, looking quite innocent, may be quite vicious in its absorptive effects and might even contain localized pockets of pus in its bed, which can only be demonstrated at the time of operation. Where tonsils of this innocent appearance are encountered, your course will be to proceed first with an exhaustive search in the other medical departments for a focus of absorption and postpone the removal of the tonsils until the other possible sources have been found negative, but continue to consider the tonsils with suspicion and potentially very vicious.

The more frequent type of chronically infected tonsil met with is the gland of moderate size, dusky red with fairly large clefts and crypts in the upper third. There will always be a pronounced band of congestion along the pillars and palate. Pressure will express a pastelike or a milky secretion; the latter we consider the most dangerous type of secretion expressed. The tonsils will usually be sensitive and the gagging reflexes quite active. These are always infected tonsils, producing systemic absorption. They should be removed whether they are causing distant symptoms or not, as the patient's health will continue to be in jeopardy as long as they remain.

Secondary tonsils, or tonsillar stumps, for which there is seldom any excuse, are one of the most vicious types of all in producing distant absorptive symptoms. Its abundance of scar tissue, organized during the process of healing after the primary partial tonsillectomy, seals the surface tightly. The superficial vascular constriction makes the remnant appear pale and innocent, but the absorption that may result is far greater than the amount of gland left would indicate. A small piece of the gland, entirely closed in, can alone keep a generalized arthritis progressing. This was shown in a number of reported cases of Dr. Snyder's with the late Dr. King some years ago. All tonsillar tabs and stumps should be eradicated, particularly if embedded. Embarrassing as it may occasionally be to tell the patient, the fact remains that tonsils cleanly removed in patients over six years old seldom recur.

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Little need be said about the adenoids and other pharyngeal lymphatics, except that they should be examined with the same thoroughness and when infected, removed as completely as

possible. It is well to remember that infected adenoid tissue is more likely to recur after removal than infected tonsils.

Histologic examination helps to confirm a correct opinion, but it is a little late in helping the preoperative diagnosis. When enough such examinations have been tabulated, they will help standardize the occurrence of infection in these different types of tonsils.

Next to establishing the guilt of the tonsil, the most important step is the correction of its vicious influence. Local treatment of chronically infected tonsils by antiseptics, with the idea of effecting its systemic absorption, is a waste of time. x-Ray therapy will shrink the tonsil but does not eliminate its contained infection. In fact positive bacterial cultures can be taken immediately following the treatment. Electrical coagulation is not efficient enough in cases of chronic arthritis where every vestige of tonsillar tissue must be removed, as the mucous membrane may grow over the small pieces of gland tissue and bury them, leaving a smooth, clean-looking fossa. The writer has seen abscess formations develop later from pieces of tonsillar tissue buried in this manner. If the tonsil is causing the arthritis, you must know it is absolutely all cleanly removed.

The most certain means of thorough eradication is the clean enucleation of the gland, removal of the plica triangularis and any lingual lymphatic tissue projecting up into the base of the tonsillar fossa.

There are very few contraindications to doing a tonsillectomy when the clinical picture clearly points to them as interfering with the health of the patient. Any other organic disturbances should be, as nearly as possible, corrected, and we know from practical clinical experience that infected tonsils are the most frequent foci of infection in cases of rheumatoid arthritis. Depending upon conditions elsewhere in the body, a choice between local and general anesthesia will make the procedure comparatively safe.

Conditions such as cardiac disease, even though some degree of decompensation is present, surprise one with the ease in which they withstand the operation. Hemorrhages now and then complicate the situation but tying all bleeding points will eliminate most postoperative hemorrhages. Secondary hemorrhages are always possible, due to infection from the mouth.

Dr. William Turnley reports 76,000 cases without a hemorrhage death. Age is not a contraindication, unless the patient is extremely infirm, as patients over fifty are often less upset by the procedure than younger people. In the past ten years at the Hospital for Ruptured and Crippled, we have done over 1800 tonsillectomies, ranging in age from one year to seventy-eight years, without a single death from any cause. If the clinical signs clearly point to the tonsils, do not hesitate to remove them. If only a uniform set of descriptive signs would be used by all investigators in tabulating their results, so that others' results could be compared, progress would be made much easier and faster for the general physician, as well as for the specialist, in finding out which signs are the most indicative and the type of tonsil most vicious in producing systemic inflammatory and toxic disturbances.

The tonsils should not be blamed for any ills without logical clinical reasons being present. The abdominal surgeon does not remove the gallbladder just because there is something wrong in the abdomen. If the tonsil is diseased, clinical signs will be found, if looked for; the history is generally significant, if thoroughly investigated, and a relationship to the distant inflammatory condition found. There has been in the past a pernicious tendency to blame the tonsils for joint and systemic disorders, whether or not clinical signs were present which pointed to it as the culprit. Remember that our knowledge of the underlying physiologic and chemical reactions of the body is still very limited, and the tonsils should not be used as a substitute just because no other cause can be found.

### CONCLUSIONS

1. Infected tonsils are probably the most frequent and important foci of infection in cases of rheumatoid arthritis.
2. They act also as frequent foci of infection in osteoarthritis. However, as these patients are generally over forty years of age, when resistance to infection is relatively high, the benefit resulting from removal of tonsils in this group of patients is relatively less, though definite, according to the age of the patient. Age in itself is not a contraindication for tonsillectomy.

3. Many innocent appearing and symptomless tonsils harbor latent infection in the crypts. In these cases it is necessary to apply pressure behind or externally to the tonsil in order to express infected material, generally from the upper pole.

4. Tonsillar stumps and remnants should be viewed with suspicion. It is not possible to be absolutely sure that all tonsillar tissue has been removed by electrocoagulation.

## CLINIC OF DR. LEE M. HURD

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### THE NASAL ACCESSORY SINUSES AS FOCI OF INFECTION IN ARTHRITIS

THE writer believes that acute or chronic sinus infection either aggravates or is the cause of many cases of chronic arthritis because he has observed many cases of arthritis in his own practice that were benefited by the eradication of sinus infection.

Snyder, Fineman and Traeger,<sup>1</sup> in a careful study of this question, show that in a series of nearly 400 consecutive cases of arthritis seen in office practice, there was some x-ray evidence of sinus infection in 68 per cent, the majority of which gave no history or subjective symptoms of sinus trouble at the time of examination. Of those who had subsequent sinus treatment, either medical or surgical, 80 per cent showed various degrees of improvement in their arthritic symptoms, which seems to prove that sinus infection is a definite cause of arthritis. The writer personally observed and treated the majority of these cases and can substantiate the statement that when the sinus infection was relieved either by conservative methods or surgery, the patient was greatly benefited, some becoming entirely free of arthritic symptoms.<sup>2</sup>

Sinus infection occurs most frequently in the cases of rheumatoid arthritis, occasionally in the mixed type, and somewhat less frequently in the osteo-arthritis group.

In the rheumatoid arthritis group where sinus infections were present (usually of the silent type), patients frequently failed to show improvement until the sinus condition was cleared up, even though every other condition that might have caused the arthritis had been excluded or corrected. Ten of

the cases on whom the writer operated have been greatly improved or freed of sinusitis and arthritis for a period of from eight to eleven years. Sixty per cent of these were classified as rheumatoid arthritis, 20 per cent as mixed type of arthritis, and 20 per cent as osteo-arthritis.

The ethmoids were always involved, most frequently in association with the maxillaries, but occasionally they were involved with the frontals or sphenoids. In some cases all the sinuses were simultaneously involved. Ethmoiditis in these cases was usually of the hyperplastic type, that is, showing evidence of thickening of the mucosa and sclerotic changes in the bony walls. Only a little mucopus was commonly found in the ethmoids. Pus was more in evidence in the maxillary sinuses. The bacteria, when cultured, were usually so mixed in type that it had no significance.

The tonsils are commonly supposed to be foci of infection of the first rank, but in this series more than two thirds of the cases had previously had tonsillectomies without benefit to the arthritis. This would lead one to believe that the tonsils had been removed because they were the more apparent and easily accessible foci, while the sinuses were overlooked to the detriment of the patient.

The majority of these patients had no subjective symptoms of sinus disease, and were not aware that they had it. About one third of the cases had purulent nasal discharge, which is often designated as a postnasal drip. Sinus headaches were rare. In view of these facts, every sinus examination of a patient suffering from arthritis should be thorough and complete. The procedure is as follows:

Examine the nose anteriorly and posteriorly to note the condition of the mucosa and the presence of secretion. Then shrink the nasal mucous membrane and transilluminate the antra and frontal sinuses. If the transillumination suggests chronic frontal or antral involvement, give particular attention to shrinkage about their orifices and again note the character of the mucosa and secretion.

The middle turbinates, with the mucosa of the middle meatus, tell much about what may be going on in the ethmoids, frontals and antra. The writer does not believe it is possible, if there is involvement of the ethmoids or frontals, to find a

middle turbinate whose membrane is clear, smooth, glistening or normal in color. The middle turbinate because it is part of the ethmoidal labyrinth, takes on the same mucosal change as the ethmoidal cells. One of the first changes noted when the ethmoids become involved is change in character of the mucosa of the middle turbinates, especially along their lower border and at the anterior and posterior ends.

Transillumination is a great aid in detecting sinus involvement in the antra and frontal sinuses, and should always be used as a routine procedure. Too much value should not be placed upon it, however, because an involved sinus may transilluminate clearly, or the reverse is also true. A sinus may transilluminate darkly, where the active process has long since subsided, if the bony walls are thick or have become thickened from a previous operation. Transillumination is of no value for the ethmoids and the sphenoids, because of their inaccessibility. For diagnosis of pathologic conditions in these sinuses we must depend upon x-ray findings and the reports of the rhinologists.

Roentgenographic studies of the paranasal sinuses should be made in all cases of arthritis, regardless of whether or not the patient has nasal symptoms. It is important that they should be well made. Poor films are worthless. They should be made in 4 stereoscopic pairs, at proper angles. These are of great value in elaborating the clinical information, but here again previous inflammations and operations may have produced fibrous thickening of the tissue which will obstruct the rays, and produce a picture similar to that of a sinus full of pus. At times, however, even good films will not always confirm the clinical findings. Finally, the x-ray films should always be interpreted in the light of the clinical evidence.

Some mild cases of sinusitis will respond to conservative treatment, and in others surgery is indicated. The treatment consists in shrinking the membranes, applying a mild silver protein solution, and douching. Vaccines may also be used which sometimes benefit the patient but many times do not. In antral infections daily douching is indicated, and if there is improvement in the character and quantity of the secretion, this treatment may clear up the infection, and operation will not be required. About 75 per cent of the cases may be

douched through the natural orifice; in the remaining 25 per cent needle puncture will be necessary.

Surgery must be resorted to if the following conditions are present:

1. Polypoid degeneration of the ethmoidal mucosa with an associated osteitis of the cell walls. This can be definitely determined by inspection and in the stereoscopic films.

2. Greatly thickened mucosa in the frontals or antra. Drainage at least should be established, but it is better to remove the infected mucosa.

3. Badly infected ethmoids that have not improved following the use of conservative methods of treatment.

The sinuses should be strongly suspected if the patient has a slight elevation of temperature; if there is profuse purulent discharge in the back of the throat; or if there are headaches related to the sinuses. When the above symptoms are present, conservative treatment is a waste of time, and only surgery will afford relief and effect a cure.

In order to be successful, an operation on the sinuses must be thorough and complete. A submucous resection of the nasal septum must be done whenever indicated, as this gives a much better view of the ethmoidal labyrinth. If the ethmoids are involved the exenteration must be complete, for if part of the cells remain the patient will be no better off than before. This is true of all the sinuses; all infected, degenerated membrane must be removed.

It is important to remember, however, that there may be an underlying cause of the sinus infection such as: (*a*) deficiency in vitamins, (*b*) allergia, or (*c*) endocrine imbalance. It is obvious, therefore, that if a cure is to be effected, the cause or causes must be determined and corrected.

A cold may precipitate a slight flare-up in a sinus but if the operation has been successfully performed and adequate drainage has been established, the infection will promptly clear up with a few treatments, and there should be no ill effect on the arthritis.

It is generally believed that a winter spent in a dry climate such as in Arizona, will cure sinus disease, but this is not always the case. A dry, mild climate frequently reduces the number and severity of upper respiratory infections, but



unless the residence is permanent, no lasting benefit will be derived.

"Once a sinus case, always a sinus case" is a pretty slogan which is prattled by the laity, and, the writer is sorry to say, by some doctors who are apparently just as ignorant of the situation as the layman. The fact is that the majority of sinus infections can be permanently cured if the sinuses are intelligently and skilfully treated.

**Summary.**—1. The nasal accessory sinuses are important factors in chronic arthritis.

2. Involvement of the sinuses often gives few or no symptoms.

3. In most of the cases in this report there was no frank pus and few headaches. These cases might be termed "silent sinusitis."

4. In refractory cases the best results were obtained by surgery.

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## CLINIC OF DR. DAVID N. BARROWS

### HOSPITAL FOR THE RUPTURED AND CRIPPLED

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#### THE FEMALE PELVIS AS A FOCUS IN ARTHRITIS

THE numerical importance of the female pelvis as a focus of infection varies directly with each group of patients studied. This is dependent directly on the frequency of past and present gonorrhea in each particular group, with its accompanying arthritides explaining this variation.

Assuming for the moment that all cases with active neisserian inflammations are eliminated, there will be found a definite proportion, probably always less than 10 per cent of female arthritis, where pelvic foci can definitely be proved to be an important cause of arthritic phenomena.

As far back as 1910, and again in 1913, the late Frank Billings drew attention to the necessity of cleaning up the cervix uteri where the focal point of infection was obscure. In a series of 60 female arthritics studied by Munro and reported in 1909, 60 per cent were found to have distinctly purulent vaginal discharges and K. S. Clark in 1908 and Bannatyne in 1904 regarded the uterus, ovaries and pelvic mucosae as potent sources of focal toxins.

Sturmdorf of this city, in 1916, in support of his enucleation operation for the cervix uteri, named the cervix "tonsil of the uterus" and, shortly after this, Friedlander drew attention to its activities as a focal point of infection. In 1923, R. L. Dickinson gave a simple anatomic explanation of its activities; *i. e.*, that its lymphatics are open spaces around the gland cells of the mucosa, opening into lymphatic channels which pass, in part, directly to the parametrium. Others connect with the lymphatics in the body of the uterus, determining parametritis and infections of the fallopian tubes and ovaries. When a

cervix becomes brawny and indurated it is easy to visualize its potentialities, but Dickinson gives us a clearer idea of why the simpler erosions, ulcers and cysts may prove to be active foci.

About twelve years ago, Moench reported experimentally from the Mayo Clinic, drawing attention to the pelvic focus and its potentialities. She cultured the deeper layer of chronically inflamed cervixes, and produced definite arthritis in inoculated animals. Some question has been raised as to the specificity of this experiment, but it was subsequently confirmed by the work of Barrett, Lash and Pillot.

Robinson in the *British Journal of Physical Medicine* as recently as 1935, as reported in the 1936 *Rheumatism Review* prepared by a committee at the request of the American Association for the Study and Control of Rheumatic Diseases, feels that infection of the uterine cervix and prostate gland is in most cases responsible for arthritis. He noted consistent improvement only when these (and other infected foci) were treated. "There is," he says, "no remedy for it except (long-wave) diathermy, *i. e.*, a wave length of 100 to 400 meters with a current frequency of  $\frac{3}{4}$  to 3 million cycles per second." This he specifies should be "given intrapelvically by special electrodes."

We all appreciate that diathermy, since its first use in medicine, has been recognized as of great value in pelvic infections and this conclusion by Robinson is in exact conformity with the experience of the early English workers, mentioned above.

It has been my privilege to make gynecologic examinations on about 4000 arthritis patients during the past ten years in one of our larger arthritis clinics, at the New York Hospital for Ruptured and Crippled. After all other contributing foci have been eliminated to the best of our ability, cases where the pelvic focus appears largely responsible seem to run between 6 and 8 per cent. In this particular group, there are very few gonorrheal cases, probably less than in the average general practice in this city. The large majority of the active pelvic foci demonstrated are: infected or eroded cervixes, fibroids of the uterus, postabortal or instrumental infections, with an occasional salpingitis and parametritis.

On our gynecologic service at Bellevue Hospital no cases of arthritis are accepted unless diagnosed as gonorrheal. Some of them turn out later to be mixed infection, but this may be a transition from one to another due to subsequent invasion of other bacteria.

As regards treatment, *i. e.*, removal of the focus, the gonorrheal, and the nongonorrheal or mixed infection form two very distinct groups.

Taking up the mixed-infection group first, we find that many of the cervical foci can be relieved by local and office treatments. One very valuable adjunct we find to be the Elliott apparatus, which raises the local pelvic temperature by insertion of a distensible vaginal rubber bag of special design through which water heated to fixed temperature is pumped for periods of one to five hours. A similar bag can be used in the rectum, *e. g.*, in prostatic cases.

We have found that many obstinate cases of pelvic inflammatory disease will respond beautifully to this medium, and we use it more extensively than pelvic diathermy.

At Bellevue Hospital it has proved very valuable in our latest modification of the hyperthermia treatment in use for neisserian infections. We have been able to obtain better results by using the Elliott apparatus to raise the local pelvic temperature to 109° or 111° F. by pumping in water at 120° F., with a general body temperature elevation of 105° to 106° F., using a heating box, than we could achieve by elevating the general body temperature to 106.8° or 107° F. Also, this combined method has proved much safer in our hands and less distressing to the patients. Local burns in the vagina have been of no moment in over five years' constant use of a half dozen machines, going practically twelve hours a day, which is quite different from our experience with local pelvic heat by radiotherm.

This modification has apparently eliminated the grave dangers of prolonged hyperthermia at effective heat levels.

If they do not respond to these simple measures, then the problem is larger. In cases where the mixed infection has passed or lies beyond the confines of the cervix, Snyder believes that it becomes deeply entrenched in the parametrium. This has proved to be the case in many of our infections follow-

ing intra-uterine instrumentation and induced abortion and although the pathology appears entirely confined to the lower uterine segment, an extensive removal of tissue by Sturmdorf enucleation up to the internal os uteri has been followed by complete disappointment in a number of cases in my hands and those of others in our clinic. For these, for fibroids of the fundus uteri, and for salpingitides of this group, removal of the uterus as a whole, by complete rather than supravaginal hysterectomy, is the most successful treatment at our hands. C. H. Mayo in 1927 apparently came to much the same conclusion, for, in speaking of the removal of the fundus uteri for focal infection, he advised the subsequent removal of the cervix if only temporary or no relief is obtained by the first procedure.

A few brief case reports where we have been able to have good follow-up data may serve well to illustrate these points.

**Case I.**—M. D., aged thirty-one, private secretary. Arthritis following criminal abortion, with badly torn and brawny, infected hypertrophied cervix. Complete invalidism from involvement of many joints of hands and legs. Gonococcus complement fixation negative. Cervical and urethral smears negative for gonococci. All other potential foci negative.

High Sturmdorf removal of cervix. No other pathology palpable.

Result: 100 per cent failure. No improvement observed in three years.

**Case II.**—M. A., aged fifty-two, housewife, infected cervix. Para 2. No history of postpartum infection. All other potential foci eliminated. Menses regular and normal amount. Crippling of hands, knees and hips. Slight improvement following office treatment.

High Sturmdorf removal of cervix. No other demonstrable pelvic pathology.

Result: 100 per cent failure. No improvement for four years.

**Case III.**—M. L., aged forty-two, uterus duplex unicornis. Fibromyomata of both fundi. Multiple joints with marked deformity. Other foci eliminated previously.

Relief after two months. Excellent result for eleven years following complete hysterectomy with bilateral salpingo-oophorectomy.

**Case IV.**—M. S., aged forty, child's nurse. Early abortion by nonsterile instrument. Other foci eliminated. Bedridden for two years. Marked deformity of the hands and feet.

Operation: complete hysterectomy with bilateral salpingo-oophorectomy

Relief after one month. Able to work for past ten years

Case V.—M. B., aged thirty-seven, ex-chorus girl.

Other foci cleaned up. Multiple points with active arthritis. History of at least 17 criminal abortions. Bilateral large hydrosalpinx.

Operation: complete hysterectomy with bilateral salpingo-oophorectomy.

Result: excellent at least five years.

Case VI.—H. H., aged forty-one, Swedish housewife. Multiple joints and deformity and peri arthritis. Multiple fibroids of the uterus. Other foci clear. Cervix small and clean. Probably not infected.

Supravaginal hysterectomy with bilateral salpingo-oophorectomy.

Result: excellent; followed for two years, then lost.

Due to difficulty of anesthesia complete hysterectomy not attempted, planning to remove cervix later.

This result we consider quite fortunate as we have seen 10 or more cases where supravaginal hysterectomy alone proved of no value.

Case VII.—E. C., aged forty-five, chambermaid in hotel.

Supravaginal hysterectomy fifteen years before for gonorrheal salpingitis. Reinfected two months previously with severe arthritis knee and hand. Smears of cervix and urethra were negative for gonorrhea on our wards. Showed mixed organisms.

Operative removal of cervix from below revealed pocket containing 5 to 7 cc. thick pus, culture negative.

Probably a "pyometra" of the upper end of cervical stump.

Result: slow but excellent for at least four years.

Knee shows limitation of motion but patient cannot take time off for orthopedic care. No arthritis since leaving hospital.

We have also treated locally 6 cases of definite recurrent adnexal complications where the arthritis improved on repeated occasions while under gynecologic treatment, one over a period of six years. None of these cases has come to operation, as they can be comfortably relieved of each attack by a few clinic visits.

All other potential foci in these cases have been pronounced negative. It must be remembered that the improvement of their general health resulting from the pelvic treatments may explain these results.

The report of the committee previously mentioned emphasized the difficulty of the diagnosis of gonorrheal arthritis. In reviewing a carefully recorded series of 85 cases reported by Kufu, Myers and Gwynn, attention was called to several points which they consider worthy of reemphasis, some of which are as follows:

"An initial polyarthralgia may resolve into a more stubborn monarthritis. . . .

"Knees, ankles, wrists, metacarpophalangeal joints and shoulders are most frequently affected. . . .

"Involvement of sternoclavicular joint is unusual." (Two out of 85; in our series of a similar number, 4.)

"Spurs of os calcis are rare" (7 in 85 cases) "confirming Von Lackum's contention (1930) that gonorrheal spurs is a misnomer."

They draw attention to the opinion of the Neisserian Medical Society of Massachusetts that an honest history and special knowledge of the relative significance of clinical and laboratory data are important.

The report published April 10, 1937, by Warren, Hinton and Bauer, working under a grant of the Rockefeller Foundation, from the medical clinic of the Massachusetts General Hospital, Harvard Medical School and Wassermann Laboratory of the Department of Health of the Commonwealth of Massachusetts emphasizes the value of the gonococcus fixation test when performed under controlled conditions. They found that tests done on the serums of 52 proved cases of gonorrheal arthritis "gave 80.7 per cent positive at all times," and they conclude that in cases where the history is consistent with a diagnosis of gonorrheal arthritis a positive test will be correct in 90 per cent of the cases. In about 20 per cent the reaction will be negative.

The committee's report regards the new culture methods utilizing "the oxydase reaction" as more accurate than smears, as described by Gordon and McLeod, 1928, and since modified until in 1934 gonococci were isolated twice as often as from smears. The complement fixation reaction for gonococcus they feel, as we do, should become a routine diagnostic procedure, Myers and Gwynn reporting positives in 86 per cent of 43 cases and McEwen, Bunim and Alexander 98 per cent of a similar series of 43.

Gonorrheal arthritis responds better than does vaginal, cervical or urethral gonorrhea to hyperthermia, but mixed infections have received little benefit in our series. Even slow duration heat treatments, especially if repeated twice or three times a week will clear the arthritis as if by magic, often



leaving the complement fixation and smears still strongly positive.

With regard to the operative treatment of arthritis caused by gonorrheal infections of the pelvic organs, we find wide differences from the mixed type right at the start. We have had a group of cases in which the gonorrheal infection of the cervix has been acute, in another subacute (six weeks to six months) and a third group which may be called chronic, *i. e.*, where the infection had persisted over a period of years with constant reinfection.

Good results have been obtained in all these groups by thorough removal of the cervix, which seems to act as the principal focus, by means of a high enucleation of all the gland-bearing tissue by Sturmdorf's operation.

Cashman at the University of Pittsburgh has obtained equally satisfactory results in acute and subacute arthritis cases by using a deep conical destruction of the gland-bearing area of the cervix by means of the actual cautery.

There is no question in our minds but that in a cervical enucleation by the Hyams' technic using surgical diathermy, less reaction should eventuate in the adjacent structures and still give an adequate result.

The removal of the cervical cone of tissue by means of the Sturmdorf procedure causes local trauma due to traction necessary for proper exposure of the indurated swollen, brawny cervix for removal. In even young multiparae this was followed by a very definite palpable thickening in the parametrium and adnexa. In spite of this distinctly outlined inflammatory reaction, the joint symptoms began to subside immediately after operation. In 2 cases in which the inflammation was fulminating and completely disabling with the patient confined to bed, pain was relieved in five days. One of these was a subacute case and another an extremely acute infection of less than two weeks' duration. After operation, the cervical smears continued positive, but the inflammation in the joints and peri-arthritic tissues subsided very rapidly.

It has been known for a long time that the gonococcus can be cultured from the fluid of swollen joints, and that it does attack the endocardium; but in the tissues of the cervix with its very large, open lymph spaces, the infection may get so

active that little in the tubes has any bearing on the arthritis, the large part of the focal poison partly arising from the fact that the toxins are locked up in the tissues of a brawny inflamed cervix. These 2 cases with their postoperative positive spread, coincident salpingitis, and parametritis, following enucleation of the cervix, and, in spite of all this, a rapid improvement of all joint symptoms, go a long way toward suggesting that the cervix is the really important focus in acute gonorrheal inflammations of the joints and surrounding tissues.

These typical cases in detail are as follows:

**Case VIII.**—A. G. M., aged thirty-seven, housewife. Three months arthritis and periartthritis especially in hips. Spreads negative. Complement fixation negative to 214 different strains of streptococci but positive for gonococcus.

Operation: old cystic cervix removed by Sturmdorf technic. Discharged, walking, five days later. Excellent result at least ten years.

**Case IX.**—L. G., aged twenty-two, maid. Gonorrhea with arthritis of clavicular joints, hands, etc. Spreads positive. Brawny infected cervix removed as above, followed by parametritis, salpingitis, but no arthritis. Spreads positive after operation.

Followed six months, excellent result.

**Case X.**—L. S., aged twenty-one, amateur prostitute, acute gonorrheal arthritis hands and feet two weeks.

Cervix indurated and swollen. Spreads positive.

Relief three days after removal of cervix as above.

Postoperative spreads positive. Parametritis. Salpingo-oophoritis, but no arthritis.

Results: excellent at least one year (lost).

## CONCLUSIONS

1. A certain group of arthritis cases in the female, probably between 6 and 10 per cent, have the most important focus in the pelvis.

2. Some of these will require operative removal.

3. Removal of the cervix in nongonorrheal cases has frequently proved disappointing in our series, as has supravaginal hysterectomy.

4. Removal of the cervical gland-bearing tissue has proved adequate in a number of gonorrheal cases.

5. C. H. Mayo has stated that a residual cervix may need removal if result is unsatisfactory following supravaginal hysterectomy, because it has left part of the focus behind.

6. Complete hysterectomy has given satisfactory results in our hands in fibromyoma uteri, in old infections of parametrium, adnexa, and myometrium, and in pelvic infections of uncertain extent—such as may arise from a badly inflamed cervix on abortion.

7. We have omitted from this discussion a large group of cases involving genito-urinary infection sometimes secondary to pressure of tumors, etc.

8. The newer cultural methods are changing the entire picture in the diagnosis of latent gonorrheal infections and rapidly making less difficult the accurate diagnosis of all gonorrheal arthritis.



## CLINIC OF DR. JOHN A. TAYLOR

### HOSPITAL FOR THE RUPTURED AND CRIPPLED

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#### THE UROLOGIC FACTOR IN THE ETIOLOGY AND TREATMENT OF ARTHRITIS

IT HAS been our privilege during the past few years to have been an integral part of the clinic of Dr. R. Garfield Snyder established exclusively for the treatment of arthritis at the Hospital for the Ruptured and Crippled. Every case coming to this division of our urologic clinic has been referred from the arthritis department. In that way we have been able to study a large number of cases of arthritis with the idea of finding a focus of infection in the genito-urinary tracts. Needless to say, all of these cases were examined by the other special departments of medicine and surgery. For the purpose of forming an opinion as to the incidence of the urologic factor in the production of arthritis we have reviewed 1000 consecutive cases seen in this clinic. Cases of frank gonorrheal arthritis are omitted from the study because that class of cases is discussed elsewhere in this symposium.

A careful urologic history is extremely important. We found that in only 5 per cent of the patients who did not admit a past or present relevant history did we succeed in finding a focus of infection. This is a valuable fact for the practitioner who must treat arthritis without the help of a highly organized clinic, for he can decide on the necessity of a urologic consultation, knowing that a negative history will, in approximately 95 per cent of the cases, exclude the genito-urinary tract as a causative factor of the arthritis. In this series, 40 per cent of the cases admitted a genito-urinary history, exclusive of lues which is discussed elsewhere. Of this 40 per cent we were able to demonstrate an infectious focus in 62 per cent of this group.

The urologic examination is always preceded by a general examination. Then an orientation examination is done which includes the examination of the external genitalia—noting particularly the epididymes and vasa for vestiges of old infection. The kidneys are palpated, noting any irregularity in size, shape, or position. The contents of the prostate and seminal vesicles are expressed after a digital examination. Sterile specimens of urine are obtained before and after massage, for regular analysis and cultures. At the time of the examination a drop of the secretion is examined under the microscope and a smear is made. If no pus is seen and the cursory examination appears to be negative, a large sound is passed, followed by the posterior instillation of silver nitrate as a provocative measure. This is followed by a subsequent examination to find any latent focus. If this be negative the patient is advised to prepare himself for excretory urograms.

The preparation for urograms which we have found most effective consists of moderate dehydration, a mild cathartic on the preceding night, an enema in the morning, following with pitressin and a rectal tube for one hour immediately preceding the series. If the urine examinations, including cultures and the slides, are negative, together with negative excretory urograms, the patient is referred back to the arthritis department, with a negative report. If the urine examinations be positive, or, if the excretory urograms show pathologic findings or be unsatisfactory, then a cystoscopic examination is made.

In the treatment of upper urinary tract infection we first attempt to increase elimination from the kidneys and bowels—the colon bacillus being a very common offender. Our results in this type of infection, with the oral administration of the various forms of mandelic acid have been almost startling. Any obstructive pathology, such as strictures at the ureteropelvic junction or in the ureters, calculi, or vesical neck obstruction is removed either transurethrally or by surgery.

In the treatment of seminal tract infection we have not been satisfied with results obtained from the oral administration of mandelic acid or any other drug. Here we need prolonged local treatment at not too frequent intervals, realizing that too vigorous a course of treatment might lead to an acute

prostatitis—sometimes with abscess formation and epididymitis. It is our habit to treat these cases not more frequently than twice a week, more often at weekly intervals. These treatments consist of a gentle stripping of the seminal vesicles and prostate, followed by the posterior instillation of various antiseptic solutions—no one solution being outstanding in all cases. Microscopic examinations of the seminal contents, and urine analysis are done at the time of each treatment.

It is in the treatment of the seminal tract infection that we have obtained the most marked symptomatic relief of arthritis. These results have corresponded with the subsidence of infection in the genital tract. We have also been able to demonstrate better the urologic factor of arthritis in these cases. We recognize a great psychic factor in the treatment of these arthritis cases, but believe there are cases which are very conclusive as to the urologic etiology, two of which we will cite. It is often very difficult to evaluate the benefits of our treatments, for most of these patients are having other forms of treatment which run concurrently—either physiotherapy, diathermy, or special treatments for other foci of infection. Therefore we are deprived of any “post hoc” argument because of the various treatments. However, we do treat some cases at a time when they are obtaining no other form of treatment. These cases have usually been pronounced urologically negative in other clinics and are sent to us only after the treatment of other foci have failed to result in the relief of symptoms.

The first case I wish to cite is that of a forty-four-year-old male who was confined to bed. He complained of pain in the muscles and joints of both shoulder girdles, in the left sternocleidomastoid and trapezius, and in the left metatarsal joints. He had been suffering with these migratory muscle and joint pains for five years—several joint regions being involved successively in each attack. The attacks usually occurred every two to three months. Following the acute pain, swelling and a mild fever usually occurred. In a search for a focus of infection he had had irrigation of his maxillary sinus, tonsillectomy, and extraction of several teeth. He had had a prostatic smear, with no pus, but a *Streptococcus faecalis* on culture. He denied any venereal infection. He had taken salicylates until a gastro-intestinal upset precluded their further usage. This was several weeks before we saw him. His present attack began one and one-half weeks previously.

His general physical examination was negative, except for painful and tender sternocleidomastoid and trapezius on the left side. There was stiffness and pain, on motion, in both shoulder girdles—more marked on the left.

The urologic examination is always preceded by a general examination. Then an orientation examination is done which includes the examination of the external genitalia—noting particularly the epididymes and vasa for vestiges of old infection. The kidneys are palpated, noting any irregularity in size, shape, or position. The contents of the prostate and seminal vesicles are expressed after a digital examination. Sterile specimens of urine are obtained before and after massage, for regular analysis and cultures. At the time of the examination a drop of the secretion is examined under the microscope and a smear is made. If no pus is seen and the cursory examination appears to be negative, a large sound is passed, followed by the posterior instillation of silver nitrate as a provocative measure. This is followed by a subsequent examination to find any latent focus. If this be negative the patient is advised to prepare himself for excretory urograms.

The preparation for urograms which we have found most effective consists of moderate dehydration, a mild cathartic on the preceding night, an enema in the morning, following with pitressin and a rectal tube for one hour immediately preceding the series. If the urine examinations, including cultures and the slides, are negative, together with negative excretory urograms, the patient is referred back to the arthritis department, with a negative report. If the urine examinations be positive, or, if the excretory urograms show pathologic findings or be unsatisfactory, then a cystoscopic examination is made.

In the treatment of upper urinary tract infection we first attempt to increase elimination from the kidneys and bowels—the colon bacillus being a very common offender. Our results in this type of infection, with the oral administration of the various forms of mandelic acid have been almost startling. Any obstructive pathology, such as strictures at the ureteropelvic junction or in the ureters, calculi, or vesical neck obstruction is removed either transurethrally or by surgery.

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was having no other form of treatment. In about six weeks he began to show subjective improvement, which coincided with the diminution of pus in the prostatic smear. The clumps of pus had disappeared, and his smear soon showed only 20 isolated pus cells per high power field. After two months he was able to go without his brace. He was very happy over the first relief that he had experienced and decided to go to a warmer climate until Spring, because of his chest condition and his arthritis. This improvement, appearing coincidentally with the clearing up of the urologic focus when he was receiving no other treatment, seems to be conclusive evidence that we were treating the primary cause of his arthritis.

**Summary.**—1. In patients who gave a negative past urologic history, only 5 per cent were found to have a focus of infection in the genito-urinary tract.

2. Forty per cent of the patients admitted a past urologic history, and of these, 65 per cent were found to have infection.

3. Cases like the two cited seem to prove that infections in the genito-urinary tract can be the sole cause of arthritis.

There was pain, on pressure, over the left metatarsus, but no swelling or redness. x-Rays of teeth and sinuses were negative. Our first examination of his prostatic and vesicle secretions showed only a few pus cells and an enterococcus. We found, however, that prostatic treatments precipitated a markedly acute arthritis, with swelling and redness in his right metatarsus. Following our first treatment, the amount of pus in his prostatic and vesicle secretion increased markedly. In a week's time we gave him another gentle treatment and found that it was followed by an acute inflammation in his wrist. This clinical response followed our treatments for three more weeks, after which they became less acute, and finally did not appear. He has been treated for several months; with a great deal of improvement in his arthritis, during which time he had no other treatment. Prior to our treatment, he had never had an interval of more than three months between attacks. This case seems to us conclusive evidence that the prostatitis and seminal vesiculitis were the predominating etiologic factors in this man's arthritis.

The second case is that of a man forty years old. He gave a history of having had gonorrhea seven years previously, without any complications. He had what he thought was adequate treatment, and was pronounced cured. He had been suffering with arthritis in his lumbar spine and left shoulder, for two years. He had been thoroughly gone over in the arthritis clinic, where a hematogenous tuberculosis of the lungs had been discovered and treated, with rest in bed, for two months. There were no tubercle bacilli in the sputum. This condition had been arrested, and he had gained weight and strength. A coccygectomy had been performed for a dislocated and painful coccyx. In spite of anti-arthritic therapy, including physiotherapy and diathermy, his lumbar arthritis had become so acute that he had to wear a back brace in order to get about. He gave no history of urinary disturbance, except that his urine had been "milky." Examinations of the urine at these times disclosed no pathologic findings except mucus.

Physical examination showed a very well-developed adult male, wearing a back brace. Without the brace his discomfort was agonizing. His reflexes were normal. There was a moderate amount of dentistry, but no apical pathology. His chest presented no abnormal signs. His heart had a normal rhythm, with sounds of good quality. The kidneys were palpable, not enlarged, or tender. There were no abdominal masses. External genitalia were negative. There was a general adenopathy, including the epitrochlear nodes. Serologic tests for lues were negative. The prostate, per rectum, was congested. The seminal vesicles were atonic and loaded with debris. A drop of this secretion was loaded with pus. A voided specimen, after massage, showed clumped pus cells with pus shreds, while the specimen before massage showed only a few pus cells. A search for tubercle bacilli in the urine was negative. Cultures of the urine showed a gram-positive diplococcus.

Excretory urograms with diodrast showed good function of the kidneys, which was equal on both sides; no distortion of the pelves; no obstructive pathology or calculi. Treatment of the prostatitis and seminal vesiculitis was carried out, with the emptying of the seminal contents once a week, followed by the posterior instillation of argyrol, acriflavine, *et al.* During this time he

was having no other form of treatment. In about six weeks he began to show subjective improvement, which coincided with the diminution of pus in the prostatic smear. The clumps of pus had disappeared, and his smear soon showed only 20 isolated pus cells per high power field. After two months he was able to go without his brace. He was very happy over the first relief that he had experienced and decided to go to a warmer climate until Spring, because of his chest condition and his arthritis. This improvement, appearing coincidentally with the clearing up of the urologic focus when he was receiving no other treatment, seems to be conclusive evidence that we were treating the primary cause of his arthritis.

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### INFECTION OF THE GALLBLADDER AS A FACTOR IN ARTHRITIS

WHEN the rôle of focal infection in the production of chronic rheumatic disease was established upon a rational research basis it was evident that infections of the gallbladder might occupy a prominent position in the etiology of arthritis. Anatomically, the gallbladder would appear to be an ideal nidus for chronic focal infection, yet it has not assumed any such preeminent position.

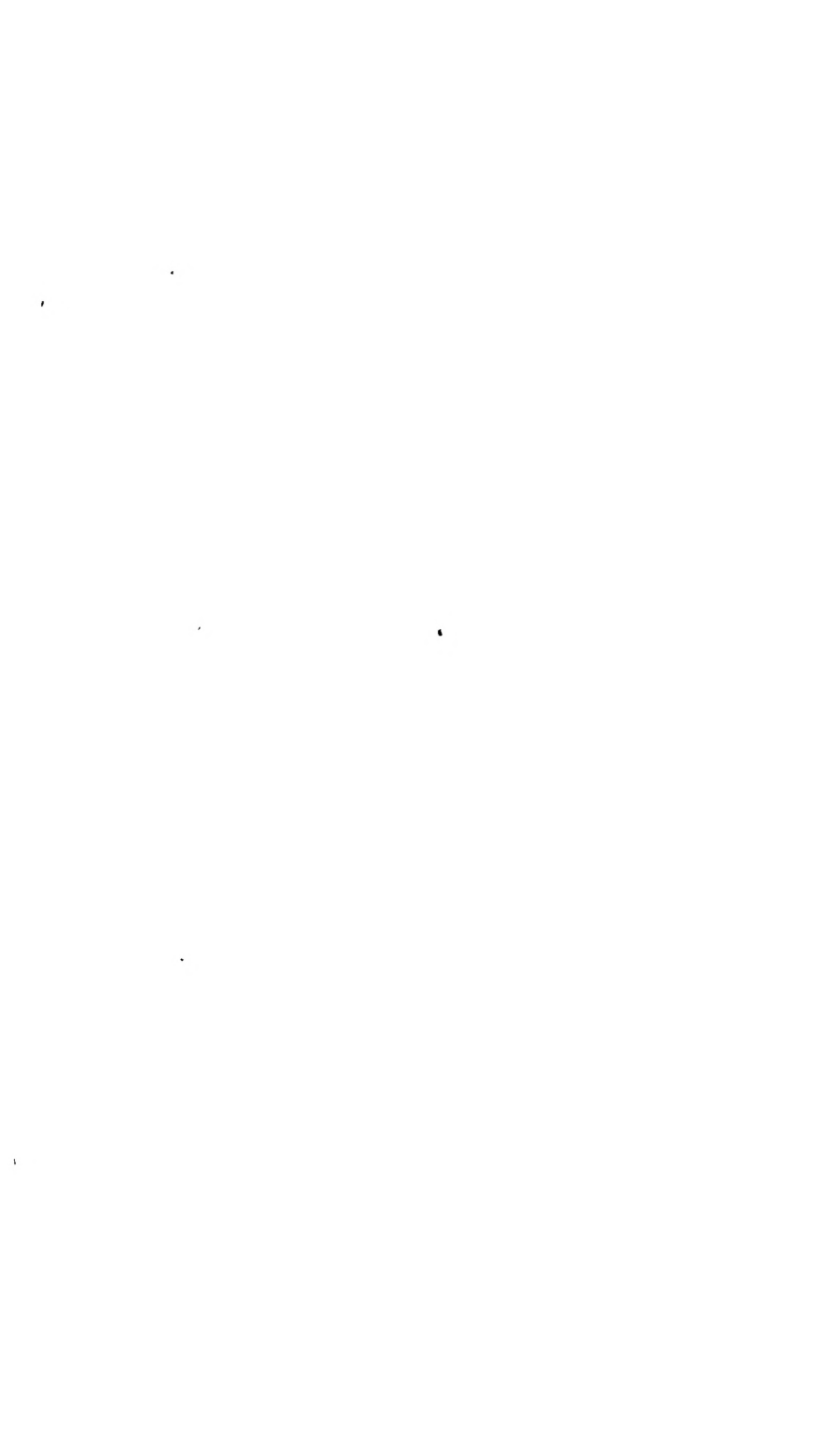
Cecil and Archer found dental sepsis in 33 per cent and tonsillar infection in 61 per cent of their patients with varying types of chronic arthritis. In a careful study, Hartung and Steinbacher, in 200 patients with chronic rheumatic disease, found only 4.5 per cent with evidence of gallbladder infection. This rate is approximately that of the common incidence of gallbladder disease in the general admission to large hospitals. Twiss and Hanssen in work primarily concerned with disease of the gallbladder considered that such relationship as exists between arthritis and disease of the gallbladder was basically infectious or metabolic. It is apparent that the juxtaposition of the liver prevents many of the general remote and metastatic phenomena of gallbladder infection. The liver interposed between the alimentary circulation and the general circulation, under normal conditions, effectively filters toxins and bacteria from the general circulation. In like manner the liver is the great detoxifying organ and bacteriolytic mechanism in infections of the gallbladder.

Increasing study indicates that the major disability of the gallbladder is due to infection in the wall of the gallbladder.

and both bacteria and their by-products drain into the liver. This infection of the wall of the gallbladder is present in at least 9 out of 10 cases of the gallbladders that are removed at laparotomy. The preeminent bacteria are derivatives of the general group of pyogenic bacteria. In the ordinary case of an infected gallbladder the physiologic competency of the liver for many years is adequate in the control of the sequelae of gallbladder infection. There ensues, however, a gradual diminution in the protective power exercised by the liver and there then begin to be general symptoms due to gallbladder disease and remote manifestations in the form of the nephropathies, cardiopathies and the arthritides. Since the liver exercises so many occult functions it is quite probable the long continued infection of the gallbladder brings about subtle changes in the biochemical mechanism of the body as well as disturbances in the general metabolism. It would appear that many individuals have long continued gallbladder infection and are sensitized or are hyperallergic from the by-products of chronic infection resulting in injury to the joints, tendons, the muscles and synovial membranes. Incidental infections provide a favorable background for arthropathic organisms that arise from points of focal infection other than the gallbladder. Our observations would seem to indicate that the infected gallbladder becomes an etiologic factor in chronic rheumatism only when and if the liver ceases to exercise its full protective capacity. It would appear that the routine removal of gallbladders in patients with chronic rheumatism is a procedure not to be countenanced. The wise procedure would be to survey the patient with chronic arthritis from the viewpoint of disabilities of the liver and biliary system per se and distinct from the arthritic symptoms. If the patient has a diseased gallbladder as recognized by a canvass of the 4 main avenues of inquiry—(1) history, (2) roentgen-ray examination, (3) duodenal drainage and (4) blood chemistry—then the decision as to whether the gallbladder should or should not be removed is entirely dependent upon the diagnosis of the local gallbladder condition.

My personal experience suggests that the patients with chronic arthritis and having a diseased gallbladder are better off by the removal of the diseased gallbladder than they would

be to continue arthritic therapy and retain an infected gallbladder. In brief, the indications for cholecystectomy in chronic arthritis are determined by the pathologic process in the gallbladder and not by the arthritis. One may reasonably expect that approximately 5 per cent of patients with chronic arthritis have a disease of the gallbladder and that in these 5 per cent either the primary or secondary infectious mechanism for arthritis resides in the gallbladder.





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THE TREATMENT OF GONORRHEAL ARTHRITIS  
BY PHYSICALLY INDUCED FEVER\*

GONORRHEAL arthritis is a metastatic lesion—the result of a blood stream invasion. It is one of the more frequent, painful complications of the disease. Although spontaneous remissions without residual damage to the joint occur, many patients suffering from gonorrheal arthritis become permanently crippled. Unfortunately, there is no study available to demonstrate how often this occurs.

Until the advent of fever therapy, a constantly increasing variety of treatments was advocated. The number and wide range of therapeutic attempts of the past indicated the failure of any individual method. Our present series of 40 cases had been treated unsuccessfully with other methods prior to fever therapy. In 1 case, removal of tubes and ovaries had not influenced the course of the gonorrheal arthritis. Chemical gonococccides, protein shock with milk, typhoid, whole blood, and intravenous chemicals had been administered in 14 of the cases. A group of 10 of our patients had received gonorrheal vaccines with no permanently beneficial results, and 2 of them were given filtrate which apparently brought on an exacerbation of their arthritis. Local diathermy, immobilization, and other procedures were of no lasting benefit to others.

**Pelvic Foci.**—Despite the prior treatment with gonococccides, all of our patients in this series had active pelvic foci.

\* Much of the clinical material referred to came from the medical services of Dr. George Baehr and Dr. B. S. Oppenheimer, and from the gynecologic service of Dr. Robert T. Frank at the Mt. Sinai Hospital. We desire to express our thanks for their kind cooperation.

In our first series of 16, the 8 females had the following: 8 cervicitis, 6 urethritis, 3 Skene's ducts, 2 adnexitis; of the 8 males, 6 had urethritis and prostatitis, 3 epididymitis, and 2 vesiculitis. In the table of 24 listed below (tabulation), all but 1 of the females had cervicitis, 7 had urethritis, 5 had adnexitis. Two of these cases had peritonitis and very severe systemic manifestations. Among the 13 males, there were 12 with urethritis, 9 with prostatitis, 2 with epididymitis and 1 with vas deferens involvement. As can be seen from the table, the extent of the pelvic involvement did not apparently affect the results. The effectiveness of fever therapy in clearing up the pelvic foci has been described previously.<sup>1, 2, 3, 4, 5</sup>

**Diagnosis.**—Every case included in this series was proved to be an arthritis of gonococcal origin. There are times when the diagnosis of such a specific arthritis presents a baffling problem. Positive bacteriologic or serologic evidence, especially from a joint, establishes the diagnosis. Yet such positive proof is sometimes lacking. Clinical hints of major importance which indicate the necessity for laboratory search for the gonococcus include the following:

(A) *Intensity of pain and inflammatory reaction.* (B) *Mono-articular involvement.* (C) *The rapidity with which the atrophy of the involved tissues progresses.*<sup>6</sup> It is usual for gonorrheal arthritis to start as a fleeting polyarthritis followed by a major involvement of one and occasionally several joints. In our 40 cases, 25 had more than one major joint involvement. Yet when one joint is the seat of an acute involvement, the presence of gonococci should be ruled out.

A patient harboring the gonococcus in the genito-urinary tract may have had or may develop a coincidental arthritis of different origin. It is this type of case which offers the greatest difficulties in diagnosis. There is no one method except recovery of the gonococcus in joint cultures or positive complement fixation of the joint fluid that can establish the diagnosis in such a case. Carpenter, Warren, *et al.*, working at Rochester University Medical School, obtained 80 per cent success with material cultured from bursae and tendon sheaths.<sup>6</sup> The most effective method of isolating cultures from the joint and the pelvic foci was described by some of their workers.<sup>7</sup> The laboratories of the Mt. Sinai Hospital use a similar technic.

Complement fixation of the joint fluid aided us in 2 cases where the organisms were not demonstrated in spreads and cultures from the genito-urinary tract and from the joints.

A positive complement fixation test on the blood is often of help when the history, spreads, and cultures fail in gonorrheal arthritis. The technic used by the Mt. Sinai laboratories under the direction of Gregory Schwartzman was recently modified.\*

Warren, Hinton and Bauer<sup>9</sup> in a thorough study of tests on 316 patients concluded that "a positive (referring to blood complement fixation) in a case in which the history is not consistent with gonorrheal arthritis is not significant. In cases with consistent history a positive will be correct in 90 per cent of the cases. In about 20 per cent of the cases, the reaction will be negative." It must be pointed out that the complement fixation test on the blood is negative when efficient drainage is established or when the formation of antibodies is retarded for other reasons. Special caution must be taken to avoid diagnostic errors when a patient with old or recent gonorrhea later develops a non-gonorrheal joint.

Perfection and standardization of the technic of complement fixation has not been achieved as yet. The findings must be interpreted in conjunction with the clinical picture and other laboratory data. Occasionally repeated tests may be of help. In general, the complement fixation should be used more often as a diagnostic aid, but cannot be relied upon as a major criterion of cure.

**Rationale.**—The progress recently made in the treatment of gonococcal infections by physically induced temperature rises has been due largely to one factor—thermolability of the gonococcus. This organism can be destroyed *in vitro* and *in vivo* at temperatures which human tissues can tolerate safely.<sup>10, 11, 4, 1</sup>

The treatment of gonorrhea and its complications by temperature reactions has long been recognized. Since Wagner-

\* The new method adopted within the past six months is known as the McNeal-Thomson test\* and is used by the New York City Board of Health. It is sensitive and allows quantitative estimation of the complement fixing bodies. A polyvalent antigen consisting of Nos. 15, 42, 8, 34, 32 Torrey strains is utilized. The 37° C. (98.6° F.) fixation method is used.

Jauregg's reports in 1918,<sup>12</sup> various methods for inducing protein shock and temperature reactions were adapted for work in gonorrhea. Satisfactory results with malaria,<sup>13, 14, 15</sup> typhoid,<sup>10, 17</sup> as well as such proteins as milk, peptone, horse serum, etc., have been reported. Local heating of pelvic organs and gonorrheal joints with diathermy also received favorable comment in the past.<sup>18, 2, 10, 20</sup> We have observed that in acute cases the local application to the joints of converse heating as obtained by diathermy and short wave currents may increase the pain and swelling.

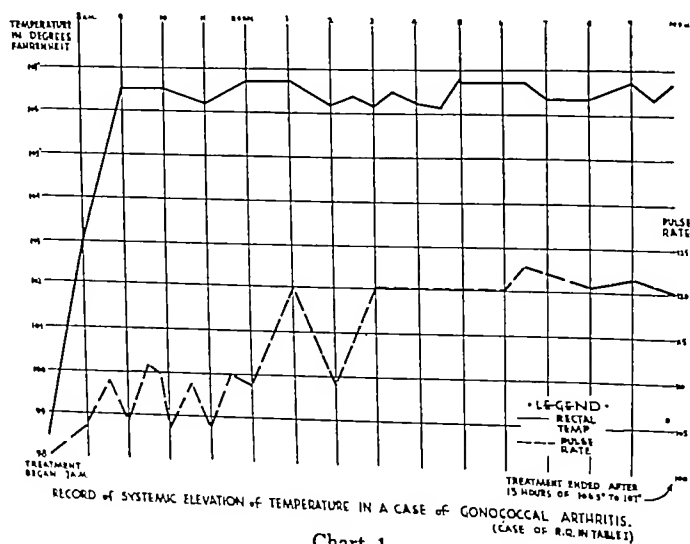
Not only can controlled effective heating be applied to the pelvic focus, but the blood stream and metastatic joint lesions can be attacked simultaneously. In addition to the devitalizing and lethal action of heat directly on the gonococcus, there are other important defensive measures evoked by fever therapy.<sup>3</sup> Simpson believes that fever stimulates immune reactions. He cites 4 cases in which patients spontaneously cleared themselves of the gonococcus within a short period after fever treatment. Certain beneficial systemic effects are also achieved with elevations of systemic temperature, such as increased speed of circulation and increased number of white cells and phagocytosis in the blood stream.<sup>21</sup>

The application of physically induced fever for gonorrheal arthritis was an important advance. It permitted the physician to control the height and duration of the patient's temperature reaction at all times. The successful application of this method in gonorrheal arthritis has been the subject of numerous recent reports.<sup>10, 22, 1, 23, 24, 5</sup>

**Technic.**—The technic developed by us was begun seven years ago. We emphasized the necessity for the production of high local temperatures in the effort to eradicate the primary pelvic focus. In this technic, the pelvic organs were heated at 108° to 110° F. for about six to eight hours while the systemic temperature was maintained at about 106° F. and permitted to endure for an additional three to four hours. This technic was a superior one for the treatment of gonococcal infections localized in the pelvis, but in gonorrheal arthritis we occasionally were able to clear only the pelvic nidus, while the metastatic focus in the joints persisted. We have more recently prolonged the period of systemic heating so that the temperature

of 106.5° F. is maintained for a period of twelve to fourteen hours (Chart 1). It is obvious that because of the thermal resistance of some strains of the organism, the higher the temperature and the longer the period of its maintenance, the greater the possibility of one-treatment cures.

For the local elevation of body temperature, we employ a combination of conductive and conversive heating. The patient is placed in what is in effect a horizontal light cabinet which covers the body from the neck down. Underneath the wooden table on which the patient lies (separated by a mattress



of about 3 inches' thickness) are placed 2 large condenser plates each measuring 12 by 14 inches. They are attached to the 6-meter short wave diathermy machine. We usually employ about one half or even a little less of the output of the machine (whose energy is rated at about 400 watts). With this technic we can usually elevate the temperature from 98.6° F. to 106.5° F. within the period of about two hours. Were we to use greater current output, it would be possible to elevate systemic temperature more rapidly. We do not do so, however, because it is our impression that most patients appear to be less uncomfortable when the temperature elevation is

gradual than when it is rapid, and also because of the danger of producing burns when too much current energy is applied.

After the systemic temperature has been raised, we are able to maintain it solely by means of the electric lamps within the cabinet. These are 12 60-watt carbon filament lamps arranged so that 2, 4, or 12 of them may be permitted to shine at one time. In order to avoid burns, should the patient inadvertently bring a foot near the electric lamps (which are guarded by wooden slats), the lower extremities are encased in leggings.

In the female, in order to achieve a more rapid gonococcal influence upon the organisms within the tissues of the pelvis, we apply additional local heating by means of the diathermy current introduced through the instrumentality of a vaginal electrode and 3 dispersive electrodes consisting of metal cuffs placed around the abdomen and around the lower extremities (first around the thighs and subsequently around the calves of the legs).<sup>1</sup>

Water is administered freely to the patients, and if they are willing to take it, 0.6 per cent salt solution. To minimize the discomfort of the treatment, we have found the hypodermic injection of  $\frac{1}{200}$  grain of hyoscine hydrobromide in conjunction with  $\frac{1}{6}$  grain of morphine sulfate to be a very effective procedure. If necessary, because of the patient's restlessness, the administration of a small dose of morphine is repeated during the treatment.

We have found the above technic a satisfactory one, but stress the point that it is strictly a hospital procedure. The only major complications have been occasional burns which, with one exception, have been mild. We consider it essential that, in addition to the nurse technician, a doctor who is experienced in this form of treatment be present during the entire period of temperature elevation. To this we attribute the absence of any major catastrophe in our series of cases.

**Clinical.**—Our cases included 21 males and 19 females, ranging from twenty-one to fifty years of age. The average number of treatments administered to the 40 cases was 2.69. Eight of them had 1 treatment, and all but 1 of these made complete recoveries. The largest number given one patient was 7. The number of treatments required is determined by the thermal resistance of the organism in a given case and by

the height and duration of temperature elevation to which the case is exposed. Lacking the facility to permit the measurement of these factors in advance of the treatment, reliance must then be placed upon the clinical response. When it becomes necessary to repeat the treatment because the thermal attack has been inadequate to destroy the organisms, subsequent treatments should be given as soon as feasible so as to prevent organisms which may have been attenuated from gaining their full virulence. Practically speaking, this means that treatments should not be spaced further than one day apart where

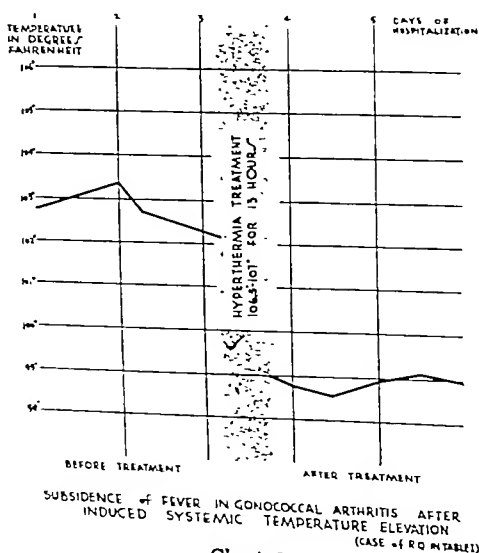


Chart 2.

possible. Some workers believe that those organisms persisting after bouts of fever become more heat resistant.<sup>25</sup>

**Response to Treatment.**—The response of the systemic and joint manifestations of nearly all of the cases to treatment was satisfactory and frequently dramatic. Temperature elevations subsided (Chart 2), malaise, chills and sweats when present disappeared. Red cell sedimentation rates showed trends to normal (Chart 3), and patients were able to get out of bed within a short period after treatment. Joint symptoms in all but 8 of the 40 subsided with remarkable uniformity immediately after the termination of the treatments. In all

Case.	Sex.	Age.	Genito-urinary focus.	Dura- tion.	Joints.	Dura- tion.	No. treat- ments.	Cured.	Marked improve- ment.	Moderate improve- ment.	Slight improve- ment or none.
A. A.	F.	31	Urethra, cer- vix.	5 mos.	Left knee.	8 wks.	3	X			
C. S.	F.	24	Urethra, cer- vix, adnexa.	3 mos.	Right ankle.	3 wks. Acute	2	X			
L. C.	F.	23	Cervix, ure- thra, adnexa.	4 mos.	Polyarthrit.	10 days Acute	2	X			
B. Si.	F.	50	Cervix, ure- thra.	5 mos.	Right ankle.	7 days Acute	1		X		
H. F.	F.	26	Cervix, ure- thra.	4 mos.	Polyarthrit.	2 mos.	3	X			
M. B.	F.	20	Adnexa.	2 yrs.	Polyarthrit.	1½ yrs.	3				X
B. K.	F.	24	Adnexa (re- moved), cer- vix.	2 yrs.	Right knee.	13 wks.	4	X			
B. Sw.	F.	22	Cervix, ad- nexa	6 mos.	Polyarthrit.	4 mos.	7				X
E. P.	F.	21	Cervix, ure- thra.	2 yrs.	Polyarthrit.	1 yr.	3	X			
L. G.	F.	24	Cervix.	1 wk.	Polyarthrit.	2 days Acute	2				X
H. W.	F.	34	Cervix, ure- thra, adnexa.	3½ mos.	Polyarthrit.	3 mos.	4	X			
R. Q.	M.	22	Urethra, pros- tate.	4 mos.	Polyarthrit.	2 mos.	1	X			



I	M	M	40	Urethra	6 wks	Polyarthrit.	1 wk. Acute	2	X		
M Go	M	35	Urethra, pros- tate	8 yrs.	Polyarthrit.	6 mos.	2	X			
M. Gr.	M.	37	Urethra, pros- tate	4 mos.	Left elbow.	1 mo. Acute	3	X			
H. W.	M.	46	Prostate.	8 yrs.	Polyarthrit.	1 mo. Acute	3	X			
G. D.	M.	35	Urethra, pros- tate.	6 mos.	Polyarthrit.	2 mos.	1	X			
I. B.	M.	39	Urethra, pros- tate epidid- ymis.	6 wks.	Left ankle.	12 days Acute	1	X			
J. F.	M.	43	Urethra.	3 mos.	Right knee.	6 wks. Acute	1	.			X
B. B.	M.	45	Urethra.	9 mos.	Right knee.	3 mos.	2		X		
H. F.	M.	34	Urethra, pros- tate, epidid- ymis.	4 mos.	Polyarthrit.	2 mos.	2		X		
J. S.	M.	41	Urethra, pros- tate, vas def- erens.	2 mos.	Left wrist.	2 wks.	6	X			
A. S.	M.	24	Urethra.	5 wks.	Polyarthrit.	8 days Acute	2	X			
S. A.	M.	27	Urethra, pros- tate.	1 yr.	Right knee.	5 mos.	2				X

cases, including these 8, there was a definite change for the better.

Of the 24 cases outlined in the tabulation, 14 had all evidence of their pelvic and joint involvements permanently eradicated within twenty-four hours after treatment. They are listed under "cured." Of the 16 previous cases, this was true of 7. The others required adjuvant treatments for varying lengths of time. These included short courses of chemical gonococicides and various procedures to speed healing of the

### SEDIMENTATION RATE CHANGES FOLLOWING FEVER THERAPY (MODIFICATION OF FAHRAEUS TECHNIQUE BY WEISS - READ IN 45 MINUTES)

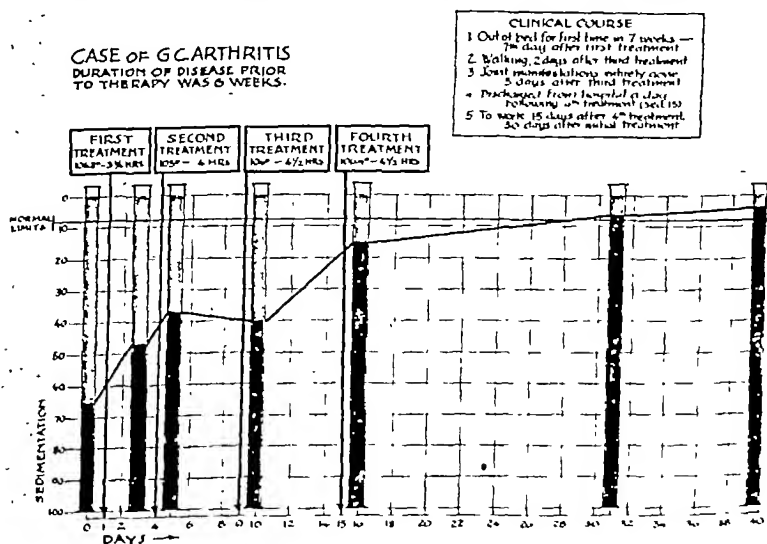


Chart 3

injured tissues of the joints. It should be noted that organisms not killed by fever appear to be attenuated so that short courses of chemical after-treatment ranging up to three weeks eliminate the original focus.

Listed under slight improvement in the table are 5 cases in which there were varying degrees of persisting pain and immobility and positive bacteriologic findings. Of the original 16, 3 cases had similar persisting symptoms. Of these 3, 1 patient required four months of after-treatment for complete restoration of painless function, and the other 2 came for treat-

ment with permanent bony ankylosis (x-ray evidence). Of the 5 in the series outlined above, one male (J. F.) refused more than one treatment. Another female (L. J.) had recurrence of pain and positive smears three weeks after discharge from the hospital. In her case, the recurrence occurred at home, and we have not yet established whether there was a reexposure with her former consort.

The remaining 3 (B. Sw., M. B., S. A.) had treatments which we now consider inadequate. Their temperature elevations were but  $105^{\circ}$  and  $106^{\circ}$  F., maintained for too short a period—five to six hours. We feel certain that these were not failures of method, but failures in our technic. Most of the 250 strains isolated by Carpenter<sup>7</sup> and his coworkers can be killed at temperatures of  $106.7^{\circ}$  F. in from eleven to twenty-one hours (75 per cent of cases). It is the rare case that requires more than twenty-one hours and becomes difficult to treat by this method. Retreatment at  $106.7^{\circ}$  F. for ten to fourteen hours should materially increase the number of rapidly cured patients.

A factor affecting response is the duration of the disease before treatment. Generally, we have found that the longer the chronicity before treatment, the less rapid is the response to treatment. The danger of permanently damaged joints also increases with chronicity. Finally, after-treatments to restore completely joint function (diathermy, short wave, baking, massage and under-water corrective exercises) are more apt to be necessary in the chronic cases.

**Follow-up.**—The importance of follow-up work in gonorrheal arthritis is self-evident. As a rule, we follow our cases for one year. The results must always be checked against time and the laboratory. One valuable aid in gauging the response is the sedimentation rate. Although the complete return to normal may take six weeks, the fall in accelerated rate is a definite indication of subsidence of the infection and inflammatory process. The delay in return to normal probably is due to the gradual absorption of residual debris and slow healing of previously acutely inflamed tissues.

**Conclusion.**—Of 40 cases of gonorrheal arthritis treated by means of temperature elevation induced by physical means described, 32 showed a dramatic restoration to normal. Eight

were complete or partial failures. In our opinion, except in those cases where the existing pathology precludes the possibility of improvement, as in bony fusion, failure is due not to the method, but to the inadequacy of the technic with which it is applied. From our experience with physically induced fever therapy, we feel that it is the treatment of choice to be used at the earliest available opportunity in gonorrheal arthritis.

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## CLINIC OF DR. SAMUEL KLEINBERG

### HOSPITAL FOR JOINT DISEASES

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#### TUBERCULOUS ARTHRITIS

IN a brief consideration of tuberculous arthritis it seems advantageous to limit oneself to a review of those elements which have practical significance. From this point of view it will be of value to discuss the diagnosis and treatment of tuberculous disease of bones and joints, for the joints are rarely involved without sooner or later an extensive invasion of the bones forming the joints.

#### DIAGNOSIS

**General Considerations.**—Tuberculous arthritis is a disease of slow and insidious onset and a chronic course. Characteristically and most often the disease is monarticular. In a minority of cases two or three joints are affected and in rare instances there may be many joints simultaneously involved. There are numerous significant factors in the patient's family and past history and in the general physical examination which contribute much to the establishment of an exact diagnosis. *First* among these is a family history of tuberculosis. An active or even an arrested tuberculosis in other members of the family with whom our patient has been in intimate contact makes it extremely likely that he has contracted the disease. Several weeks ago I saw a child six years old with an arthritis of the left knee. No other joints were involved and the x-ray film of the left knee was negative. But the history revealed that this patient's father had died and a younger brother was now ill of pulmonary tuberculosis. It was, therefore, more than likely that the disease of the left knee was tuberculous. *Second* is a history of preexisting or coexisting tuberculous disease in other

tissues. A year ago a man was referred to me for an arthritis of one knee. The history showed that this man had had Pott's disease which was arrested by a spinal fusion and a tuberculous kidney which had been removed. This information compelled the suspicion of tuberculous disease of the knee. This was confirmed at operation. *Third*, since a tuberculous arthritis is but a local manifestation of a systemic disease, there may be x-ray evidence of present or past pulmonary invasion or disease of the hilar glands. *Fourth*, the occurrence, especially in children, of some acute debilitating illness as measles or scarlet fever is likely to be followed by the appearance of a tuberculous focus. *Fifth*, trauma to a joint predisposes it to a tuberculous process. All statistics are in accord that there is a history of a definite trauma in about 50 per cent of bone and joint tuberculosis. *Sixth*, the location of the arthritis helps in the differential diagnosis. An inflammation of a temporomaxillary joint is, as a matter of experience, not likely to be tuberculous, while a chronic destructive inflammation of the spine, hip or knee, in the absence of manifest evidence to the contrary, is very apt to be tuberculous.

#### CLINICAL SYMPTOMATOLOGY

**Pott's Disease.**—Pott's disease or tuberculous spondylitis is the most common of all tuberculous bone and joint lesions. The most significant early subjective symptoms are pain in the back, weakness of the back and awkwardness in walking. Objectively we find an angular projection of the spine at the site of the disease, muscle spasm, rigidity of the spine and tenderness to pressure over the diseased area. The symptoms vary in their appearance and degree according to the location of the lesion. In the dorsal or most common site the deformity may progress to a very noticeable degree before the subjective symptoms become evident. The deformity or kyphos may be the first symptom to be observed. In the cervical region, on the other hand, where there is very free motion, even a small lesion leads to marked symptoms. In the lumbar region, too, the subjective symptoms appear earlier than the objective changes. As the disease advances the deformity increases. In the dorsal area as many as 6 or 8 vertebrae may be diseased. With their collapse a marked angulation of the spine takes



place, the trunk is shortened and the chest may be telescoped into the pelvis.

The two most frequent complications in Pott's disease are abscesses and paralysis. An abscess forming about the diseased area seeks an outlet along the tissues that offer the least resistance. Thus in the cervical area the abscess may appear in the retropharyngeal space or in the lateral aspect of the



Fig. 119.—Dorsal Pott's disease. Shows marked kyphos. Support by the hands and by plaster leg bandages indicates that this boy had had paralysis from which he is recovering.

neck. In the dorsal region the abscess may remain in the vicinity of the diseased vertebrae or burrow down along the front of the spine. Commonly the abscess extends downward and forms a psoas abscess, raising the psoas muscle from the ilium and causing a flexion contraction at the hip. It may extend under Poupart's ligament and appear in the thigh. Not infrequently the abscess extends posteriorly and is found

on the back. In the lumbar region the abscess may extend backward into the loin or buttock or downward under the psoas and into the thigh. Psoas abscesses may reach very large proportions, filling the lower abdominal quadrants and causing marked bulging of the abdomen.

Paralysis appears most commonly in dorsal Pott's disease. It is due to invasion of the spinal canal and pressure on the cord by tuberculous granulation tissue, inflammation of the meninges or a "cold" abscess. The earliest evidence is weakness of the lower limbs, instability in walking, exaggeration of the patellar and ankle reflexes with marked ankle clonus. If the disease is below the reflex center of the legs the paralysis is

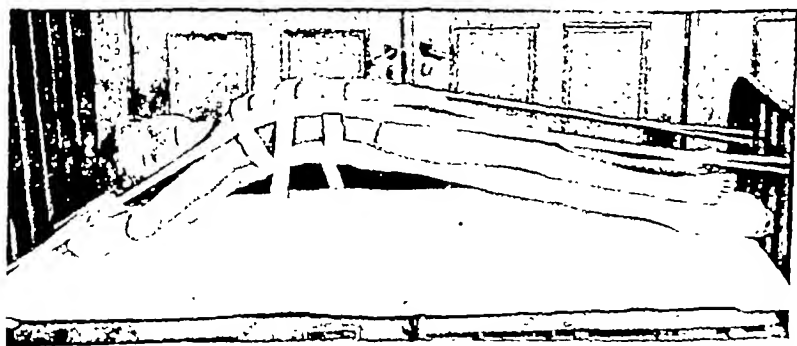


Fig. 120.—Convex frame used for the support and correction of Pott's disease.

flaccid with complete loss of all reflexes. The extent of the paralysis is not related to the degree of the deformity.

**Hip.**—The earliest symptoms are lameness, disinclination to be active and pain in the thigh and knee. The pain in the knee is due to pressure on the obturator and anterior crural nerves which are distributed in the thigh. Early in the disease the symptoms are present only when the child first begins to walk and disappear after an hour or two. After some months, however, the symptoms are continuous and increasingly disabling. A limp appears very early. The limp and disability are due in the primary stage to sensitiveness of the hip on weight bearing and in the later period to the deformity arising from fixed flexion of the hip and shortening of the limb. There is a variable degree of limitation of all motions. Muscle spasm

becomes specially apparent on attempting to move the limb. There is a fulness in the groin and sensitiveness to pressure over the hip, particularly anteriorly. One or more abscesses may appear. These usually point anteriorly or laterally, but also occasionally in the buttock.

An x-ray picture of the hip will show at first an indistinctness of the bony outlines. Later there is an irregular destruc-



Fig. 121.—Nov. 2, 1931. Extensive tuberculous process of the hip. Femoral head almost completely absorbed. Acetabulum is diseased and enlarged

tion and absorption of the femoral head. The whole of the femoral head may disappear and even part of the neck may be destroyed. The acetabulum may be invaded, usually the upper part becomes irregularly destroyed and enlarged, permitting upward displacement and even dislocation of the femur.

**Knee.**—As in other joints the disease appears insidiously and progresses slowly. The knee becomes swollen and painful, causing a limp and disability. Night cries are common in

children. As fluid accumulates in the joint the knee becomes flexed and this deformity remains unless corrected. There is usually local heat and tenderness to pressure over the knee. There is marked muscle spasm and restriction of motion. As the disease increases the knee becomes more flexed and deformed. The leg may be subluxated backward. The x-ray pictures show in the early stage only a general haziness. Later there is seen a subchondral rarefaction and destruction and absorption of the articular cartilage of the femur and tibia.

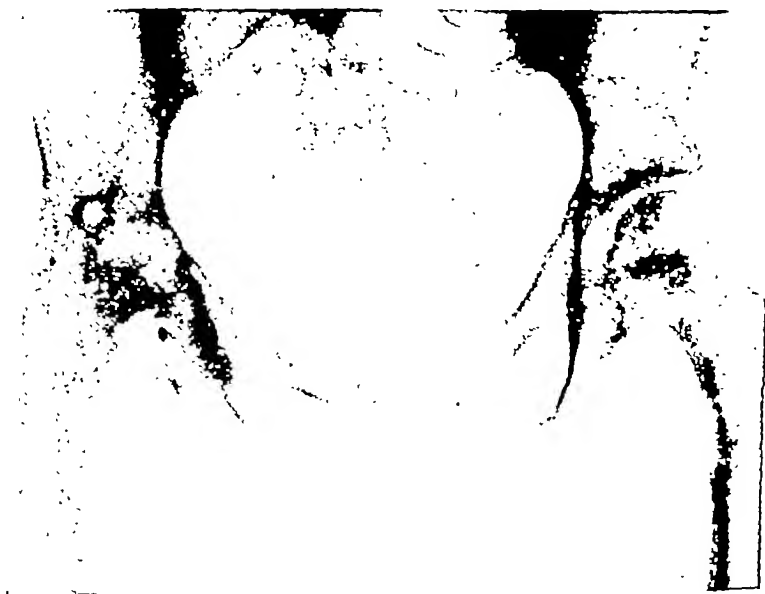


Fig. 122.—Nov. 5, 1935. Same patient as in Fig. 121. Shows healing effects of fusion of the hip joint

The patella is involved very late and always to a much less degree than either the tibia or femur. In the last stages one sees irregular excavations in the condyles of the femur and the tuberosities of the tibia.

**Ankle.**—Tuberculous disease in the ankle joint is less frequent than in the other weight-bearing joints. Its onset and course are similar to those in the knee. The ankle becomes slowly enlarged and increasingly painful. There is a limp. Muscle spasm is present, limiting motion. There is local heat

and tenderness. Abscesses may rupture leaving sinuses. The foot tends to become fixed in plantar flexion. The x-ray picture shows haziness at first and later a variable degree of destruction of the adjacent surfaces of the tibia and astragalus. The tuberculous disease commonly invades the bones of the ankle joint but may involve any or several of the tarsal bones.



Fig. 123.—Tuberculous disease of the knee. Shows extensive erosion of femoral condyles and tibial tuberosities.

**Shoulder.**—This joint is affected much less often than the weight-bearing joints. Clinically the joint becomes swollen, stiff and painful. There is marked muscle atrophy and limitation of motion. Abscesses do not often appear, hence the disease is sometimes called "caries sicca." As the lesion advances, the arm becomes fixed to the side of the chest with complete loss of abduction. In the early stages the x-ray picture is not characteristic of any disease. The head of the humerus appears mottled and the articular surfaces undisturbed. Later the



Fig. 124.—Caries sicca of shoulder. Extensive destruction of humerus and glenoid process of scapula.



Fig. 125.—Extensive tuberculosis of elbow. Shows marked erosion of humerus, ulna and radius

roentgenogram shows a destructive process in the head of the humerus and the glenoid process of the scapula.

**Elbow.**—There is a tendency in this joint for early extensive bone destruction and abscess formation. The symptoms are similar to those in other joints. There is persistent and increasing swelling and pain, muscle spasm, limitation of motion, local heat and tenderness. The x-ray picture in the early stages may be negative, except for infiltration and swelling of the soft tissues. In the later stages one sees all gradations of bone destruction in the adjacent articular extremities of the humerus and ulna and lastly of the radius.

**Wrist.**—This joint is comparatively rarely affected by tuberculosis. Its clinical symptomatology includes swelling, pain, disability, local heat, tenderness and atrophy of the hand and forearm. The roentgenogram in the early stages is negative, but as the disease advances it shows bone destruction involving the radius, ulna and several of the carpal bones.

#### LABORATORY AIDS IN DIAGNOSIS

The clinical picture in a chronically inflamed joint may present strong presumptive evidence of tuberculous disease. The roentgenogram may show a destructive bone lesion which confirms the suspicion of tuberculosis. But we should attempt to establish a positive diagnosis, for in certain joints, particularly in adults, a positive diagnosis of tuberculous arthritis warrants a major operation as a means of arresting or eradicating the local process. The measures at our command for establishing a positive diagnosis are the following:

1. **Tuberculin Tests.**—There are 3 tuberculin tests, namely, the von Pirquet or epidermal, the Mantoux or intradermal and the subcutaneous injection of diluted old tuberculin. A positive epidermal or intradermal test means that the individual has an active or latent tuberculous focus. It does not signify that the inflamed joint under consideration is tuberculous, but it is extremely likely to be so, especially if the clinical evidence points in that direction. The subcutaneous test, when positive, yields a local reaction, a systemic response by a rise in temperature and malaise and, significantly, a focal reaction by a temporary increase of the symptoms in the suspected joint.

2. **Aspiration of Fluid from the Joint.**—Whenever possible some fluid ought to be aspirated from the joint. It may

reveal tubercle bacilli and thereby establish the diagnosis. If no tubercle bacilli are found the fluid ought to be injected into a guinea-pig.

**3. Guinea-pig Injection.**—The guinea-pig is very susceptible to tuberculous infection. The fluid removed from an abscess or preferably from the joint is injected into the abdomen of the guinea-pig. If the fluid is tuberculous the guinea-pig will develop tuberculosis and succumb to it. Microscopic examination of the organs of the animal will reveal tuberculosis.

**4. Biopsy.**—This involves exposing the diseased tissue by operation and requires at least a local and often a general anesthetic. It, therefore, should be resorted to only when the other tests fail or are inconclusive and the proposed therapy is predicated on an absolute diagnosis. A biopsy permits visual inspection of the joint and removal of tissue for microscopic investigation. This test when positive is helpful. Yet conceivably the lesion may be tuberculous but the particular specimen removed may not contain either tubercles or tubercle bacilli.

### TREATMENT

The treatment of tuberculous arthritis falls into two divisions, namely, general and local.

**General.**—As tuberculous arthritis is but a local manifestation of a systemic infection, the patient must primarily and continuously receive the therapy that is appropriate and necessary for all cases of tuberculosis. This includes rest of the body and mind, forced feeding, an abundance of fresh air, and if possible living continuously outdoors.

**Heliotherapy.**—Heliotherapy, by gradually increased exposure of the whole body to either the sun's rays or to artificial ultraviolet rays, is today accepted as an important modality for improving the body tone and increasing the patient's resistance to tuberculosis. Not all are in accord with Dr. Rollier of Switzerland, the distinguished and notable exponent of heliotherapy, who believes that the sun's rays are specific in curing tuberculosis. Dr. Lo Grasso of this country is also an ardent advocate of heliotherapy properly administered and in combination with supportive and medical treatment. My experience convinces me that there is unquestionably a whole-



some and tonic effect from a well-regulated system of air and sun baths which increases the resistance to disease.

**Local Treatment.**—All local treatment has 3 objectives: (1) arrest of the disease, (2) reduction of the existing deformity, (3) prevention of increase of deformity. These objectives are obtained by immobilization of the diseased area and the application of various corrective measures by traction, postural treatment, manipulative procedures and operations. The local treatment is best considered in relation to each joint.

**Pott's Disease.**—The essential in the treatment is rest of the diseased vertebrae. In children it is best obtained by keeping the patient on a convex frame in hyperextension. This position prevents increase of the deformity and is simultaneously effective in reducing the deformity. Furthermore, the recumbent position removes the irritating and crushing effects of the superincumbent weight of the spine and trunk on the diseased area, present when the patient is standing. Instead of a convex frame one may use sand bags, a plaster bed or a plaster jacket. Many surgeons advocate a fusion operation on the spine at all ages to provide an internal splint. Experience, however, shows that in children such an operation does not cure the disease. Unless the trunk is supported and protected adequately for a very long time the disease will continue and the deformity increase. Consequently in Pott's disease in children we must depend chiefly upon prolonged immobilization for the arrest of the disease.

In an adult with Pott's disease a spine fusion is advisable as soon as the diagnosis is established. The effect of the operation is very different from that in a child. Actual fusion of the vertebrae is readily obtained and favors a rapid arrest of the disease. Subsequently the spine ought to be protected by external apparatus for at least a year.

**Complications of Pott's Disease.**—*Abscesses.*—When these are small and cause no annoyance no treatment is necessary. When the abscess is large or threatens to rupture it should be emptied, preferably by aspiration, repeated as often as may be required. If the contents of the abscess are so thick that they cannot be removed by aspiration, an incision is permissible, but the wound must be promptly sealed by suture. When sinuses appear they are best treated by simple surgical

dressings. This simple treatment of cold abscesses and tuberculous sinuses applies wherever and whenever they are found.

*Paralysis.*—This infrequent complication of Pott's disease is most effectively treated by placing the patient, child or adult, in bed, preferably on a convex frame. Recovery fortunately occurs in most cases in one to six months. In the exceptional instance it may be necessary to do a laminectomy for relief of pressure on the cord.

*Hip.*—The chief element in the treatment is rest of the joint. This can be obtained by keeping the patient in bed, splinting the hip by a plaster support and applying traction to separate the diseased surfaces. Immobilization of the hip prevents increase of the deformity. When there is a flexion and adduction deformity this may be corrected by traction or by gentle manipulation under an anesthetic. The conservative local treatment for the hip must be continued, as in the case of the spine, over many months and years, until all symptoms subside and there is radiographic evidence of fusion of the femur and ilium. Our aim must be to obtain a bony fusion, for so long as there is any motion in the hip relapse is likely and deformity inevitable.

Appreciating the importance of eliminating all motion in tuberculosis of the hip, fusion by operation is now very extensively practiced at all ages, even in very young children. Experience proves that a fusion of the hip favors arrest of the disease. It is sometimes difficult to obtain a fusion, especially in children, but we should seek to obtain it through an operation unless this is contraindicated. In the adolescent and in the adult with tuberculosis of the hip it should be our primary aim to perform the operation as soon as possible. Healing occurs rapidly in these tissues and the outlook for arrest of the disease is even more favorable than in children. Abscesses are a common complication and should be treated expectantly until by their size they cause inconvenience or they threaten to rupture, when they must be aspirated.

*Knee.*—In the adult the ideal treatment is an arthrodesis, that is, an operation for the eradication of the disease by removing the articular ends of the femur and tibia and contacting healthy bone. The bones become united and the diseased process subsides. We may confidently look forward to an ar-

rest of the local process within six months, permitting the individual to return to a gainful occupation within a year. In the young child it is difficult to obtain bony fusion. In addition there is the disadvantage of disturbing the epiphyses by the operation and thus causing a shortening of the limb. It seems best, therefore, in very young children to adhere to a conservative program. The knee ought to be immobilized either in a brace or in a plaster support, and the period of immobilization continued for many months and years. During this period one has to be on his guard to maintain the knee in complete extension, for there is a strong tendency for it to become flexed. If there is already a flexion deformity this should be corrected by traction or by gentle manipulation under an anesthetic. Tuberculous or "cold" abscesses about the knee occur fairly frequently and should be treated expectantly, as they are in other parts of the body. When they reach a size that blocks motion or when they show signs of impending rupture they should be aspirated.

**Shoulder.**—In children the arm should be supported by some form of abduction apparatus, holding the limb in about 70 degrees of abduction at the shoulder, slight outward rotation and slight flexion. The immobilization should be continued for several years, if necessary, until there are no signs of any active inflammation and the joint appears to be securely ankylosed. In the adult the treatment of choice is an arthrodesis. When the humerus and scapula are fused the inflammation of the surrounding tissues subsides rapidly and the individual is left with a very useful limb. The loss of motion in the shoulder causes only moderate inconvenience since it is replaced by a compensatory range of scapulothoracic motion.

**Elbow.**—Since disturbance of the various epiphyses about this joint would cause serious loss of substance and length in the arm and forearm, it is advisable, in children, to adhere to a program of conservative treatment, carried out by rest and immobilization of the elbow in flexion, which is for the elbow a useful position. When abscesses and sinuses appear they should be treated in the same manner as was outlined for other joints. In the adult tuberculosis of the elbow should be treated by an arthrodesis, fusing the joint in flexion. This is a sound treatment and yields good results. In this nonweight-bearing

joint some splendid results have been obtained by a wide excision of the diseased portions of the humerus, radius and ulna, leaving a pseudarthrosis. By this operation we gain 2 things, namely, the diseased tissue is removed, and a satisfactory range of motion is retained. The decision as to which operation shall be performed must be left to a conference with the patient, and depends in a large measure upon the patient's social and economic status and occupation. In a laborer an ankylosis is by far the more desirable choice. On the other hand, for a young woman not engaged in strenuous work, an excision of the diseased tissue permitting a useful range of motion may be the best form of treatment.

**Wrist.**—In children, conservative treatment by support of the forearm and hand by a splint or brace is the only treatment permissible, since any kind of surgery would result in permanent damage of the bones and permanent disability. Often tuberculosis of the wrist is but a part of an extensive tuberculous arthritis and none but conservative measures may be warranted. In the adult, if the disease is limited to the wrist and there are no contraindications, an operation for arthrodesing the wrist is permissible.

#### SUMMARY

Tuberculous arthritis is a disease of common occurrence. Of 4626 orthopedic cases admitted to the indoor services of the Hospital for Joint Diseases during 1934 and 1935, 22 per cent had tuberculous lesions. Our primary aim must be to establish a positive diagnosis. This is accomplished by correlating the history of the course of the lesion, the patient's family history, the patient's past history, the clinical manifestations of the arthritis and the results of the laboratory tests. When a positive diagnosis has been made, treatment is promptly instituted. This consists of *general measures* for the enhancement of the patient's resistance, *heliotherapy* for its tonic effects and for whatever specific healing influence it may have on the tuberculous lesion and *local therapy* to the affected joint. The details of the local treatment depend on the joint involved. We seek primarily to rest the joint by prolonged immobilization, since freedom from function favors healing of the inflammation. Sometimes, as in the spine in adults, it is possible by an

operation to provide an internal splint. This assures fixation and rest of the joint which favors an arrest of the disease. In some joints as in the knee and elbow one can eradicate by operation most of the diseased tissue which hastens the process of healing. The main element, however, in the treatment of the majority of cases is long-continued protection of the joint by some form of apparatus.



## CONTRIBUTION BY DR. HENRY T. CHICKERING

### NEW YORK CITY

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#### PNEUMOCOCCAL ARTHRITIS

PNEUMOCOCCAL infection of the joints is an extremely rare condition occurring only about once in 1000 cases of pneumonia. Bulkley<sup>1</sup> in 1914 compiled 173 cases from all available sources. In one series there were 17 joints in 12,400 cases of pneumonia. During the period from 1918 to 1932 at Guy's Hospital, Fagge<sup>2</sup> found only 7 cases. Cecil, Baldwin and Larsen<sup>3</sup> reported the occurrence of 8 pneumococcal joint infections in 1913 cases of pneumonia. Of these, 5 were due to pneumococcus type 1, 1 to pneumococcus type 3 and 2 to pneumococcus group 4. At the Hospital of the Rockefeller Institute over a period of twenty-five years only 2 infected pneumococcal joints, 1 pneumococcus type 1 and 1 pneumococcus type 3, were noted in about 1800 cases of pneumonia. There was 1 other case noted, an atypical type 2 infection adjacent to a shoulder joint but not penetrating the joint.

Cameron<sup>4</sup> has reported the occasional occurrence of pneumococcal arthritis in young infants. Many joints may be involved simultaneously or in succession.

Most of the cases of pneumococcal arthritis occur as a complication of pneumonia. A small proportion occur in association with pneumococcal septicemia without pneumonia. As a complication of pneumonia, usually one joint is involved, the knees most commonly, more rarely the shoulders, wrists and elbows.

In pneumonia, when a joint becomes red, tender and swollen, a metastatic infection may be expected and aspiration of the joint confirms the diagnosis. There are no signs or symptoms which enable one to diagnose a pneumococcal joint from any other type of acute arthritis.

Most cases showing this complication are critically ill and not only the pneumonia itself, but other complications as meningitis and pericarditis cause the death of the patient. In the very rare case where the patient survives the pneumonia and in those cases without pneumonia, recovery takes place with complete restoration of joint function.

When the joint is aspirated, direct smears of the purulent fluid as well as cultures on blood agar should be made. Occasionally sterile cultures are obtained on early aspiration of the joint and repeated aspirations may be necessary to establish the diagnosis.

Previous joint trauma may be a factor in the localization of the infection as in Fagge's<sup>2</sup> case of a young man, who after spraining an ankle and then acquiring an upper respiratory infection, developed a pneumococcal abscess of the affected ankle.

Farah<sup>5</sup> described a very unusual case of a man who, over a period of ten years, had recurrent attacks of arthritis in one of which pneumococcus type 3 was recovered from the blood. He made a complete recovery and though aspiration of the affected joints was not permitted, serologic examinations seemed to confirm the diagnosis. It is possible that the joint symptoms in this case were allergic and not a true infection of the joints.

If aspiration and later surgical drainage of the infected joint are not instituted, the intense inflammatory reaction of the synovial membrane goes on to thickening of the subsynovial fibrous tissue and destruction of the synovial surface cells and cartilage may ensue. On the other hand, with adequate treatment, no permanent joint or bony changes may take place and there is no final functional disability.

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## CLINIC OF DR. CARLISLE S. BOYD

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#### ARTHRITIS OF SCARLET FEVER

ARTHRITIS is not an infrequent complication of scarlet fever. It is often spoken of as "scarlatinal rheumatism" or "arthritis of scarlet fever." This type of arthritis is of a non-suppurative nature. The lesion consists of involvement of the synovial membrane, with a slight amount of serous effusion into the joint and some periarticular swelling and thickening. The fluid is sterile.

In 5549 cases of scarlet fever seen at the Willard Parker Hospital during the four years, 1933 to 1936 inclusive, there were 99 cases of arthritis. This does not include cases of arthritis due to serum sickness or caused by rheumatism. The incidence of the scarlet fever arthritis was as follows:

	<i>Total Scarlet Fever Patients</i>	<i>Cases of Arthritis</i>	<i>Percentage</i>
1933	1056	23	2.18
1934	1349	39	2.89
1935	1672	23	1.37
1936	1472	14	0.95

The incidence for the total cases was 1.78 per cent. Excluding the year 1936, when convalescent serum was used in many cases, its occurrence in 4077 cases was 2 per cent.

It is recognized that the frequency of this complication varies in different epidemics. The figures given here are much lower than those cited by many writers. The use of scarlet fever antitoxin or convalescent serum in the severer cases and the fact that scarlet fever in New York is much milder than it was ten or more years ago would explain the low incidence in this series as compared with older statistics.

This complication occurs more often in older children and adults than in early childhood. Although the number of cases of scarlet fever in patients ten years of age and under is more than twice that seen in those over ten years of age, there were only 40 cases of arthritis in that age group, whereas there were 59 cases in older patients. It occurs more often in females than in males; there were 70 cases in females and 29 in males.

While arthritis may occur any time in the course of the disease, it usually makes its appearance at the latter part of the first week or early in the second week—most often from the fourth to the tenth day. The joints most frequently involved are the small joints of the hands, wrists and knees, less often the shoulders and ankles and occasionally the elbows and hips. The tendency is for symmetrical joints to become involved either simultaneously or one shortly after the other. Sometimes as the pain lessens or disappears in the joints first attacked, other joints become affected. Rarely, after subsidence of the condition, in a week or more there is a recurrence, which is usually of shorter duration than the initial attack. In this series, the average number of joints involved was three or four.

Pain is the most characteristic symptom and varies in severity. In some cases it may be accompanied merely by fever. The pain is usually fairly severe and is increased by active or passive motion of the involved joints. Some complain of moderate pain and stiffness and but little tenderness. In other cases, in addition to the pain, there is more or less definite swelling and a certain amount of tenderness. There is some effusion into the joint and a variable amount of periarticular involvement. Increased heat or redness may be present. When the hands are involved, tenosynovitis is not infrequently seen. Fever is a rather constant accompaniment of the joint involvement. There is usually a steplike rise to  $101^{\circ}$  to  $102^{\circ}$  F., then in mild cases the temperature is remittent and in the severer cases maintained at  $102^{\circ}$  to  $103^{\circ}$  F., with a return to normal by lysis. At times the elevation of temperature occurs from six to eighteen hours before the patient complains of pain or any evidence of joint involvement is noted. More often it occurs about the time that the patient complains of joint pains and lasts until the joint symptoms subside.

The duration of the arthritis is usually from two to five days. In exceptional cases it may last for two weeks. The cases which develop early in the disease are usually more severe than the later ones.

Treatment consists of rest of the affected joints, methyl salicylate externally and the internal administration of salicylates. Locally, relief is usually afforded by the application of gauze saturated with methyl salicylate 1 part, olive oil 5 parts, or an ointment such as:

R Methyl salicylate	2½ drachms
Petrolati	q. s. ad. 2 ounces

spread on a piece of linen or several thicknesses of gauze and placed over the affected joints, which are then wrapped with nonabsorbent cotton or cotton batting or flannel. The affected parts should be supported in the most comfortable position by means of pillows, small cushions or bath towels.

Salicylic acid preparations have proved of value in relieving this condition. A child five years of age may be given sodium salicylate 5 grains every three or four hours; a child of ten years, 10 grains every three or four hours; an adult, 20 grains every three hours. An equal amount of sodium bicarbonate may be given with the sodium salicylate. Salicylates should be given well diluted and not on an empty stomach. When sodium salicylate is not tolerated by the stomach, acetylsalicylic acid (aspirin) may be used. A five-year-old child may be given 5 grains every three or four hours; a ten-year-old child, 7½ grains every three or four hours; an adult, 10 grains every two or three hours. The dosage of these drugs must be guided by the effect produced. As the symptoms subside, the dose should be lessened. When salicylates are not borne by the stomach, they may be administered by rectum. Then the daily amount of the drug may be divided into two doses and given morning and evening. The patient should receive a saline enema and one-half hour later the salicylate mixed with 4 ounces of starch paste should be given slowly into the rectum, using a funnel and small rectal tube or catheter.

#### DISCUSSION

There is a difference of opinion as to whether or not the joint involvement in scarlet fever is a manifestation of rheu-

matism. The arthritis of scarlet fever is more prone to attack the smaller joints than is rheumatism. In the 40 cases in children ten years of age and younger, 110 joints were involved. The hands, wrists and ankles accounted for 78 of the 110 joints. The most common manifestation of rheumatic disease in children is endocarditis. If the arthritis seen in scarlet fever was of rheumatic origin one would expect endocarditis to be frequent. Not a single case was seen as a complication of scarlet fever in this series. Furthermore, in a rather extensive experience, the writer has never seen a case of endocarditis caused by scarlet fever as such, although rare cases have been reported.

A patient with active rheumatic fever may contract scarlet fever just as may any individual; then no definite relationship between the two diseases can be said to exist. The writer has seen many patients with chronic rheumatic cardiac disease pass through scarlet fever without active rheumatic manifestations. Occasionally, however, we see an activation of definite rheumatic disease during the course of scarlet fever. A child may show no evidence of rheumatic fever at the time of occurrence of scarlet fever and either during the course of or immediately following scarlet fever may develop rheumatic cardiac disease. This may be explained by the activation of a latent rheumatic disease by the streptococcus of scarlet fever. Two such cases were seen on my pediatric service at the New York City Hospital during the past two years. One case came to autopsy. Much further study and follow-up of patients is required before the relationship of the two diseases can be definitely answered.

It is my belief that endocarditis occurring in the course of scarlet fever is almost invariably of rheumatic origin and a careful study of the history, course and follow-up will prove it to be such. The rare exception may be an endocarditis, part of a pancarditis, in septicemic cases. The writer believes this nonsuppurative type of arthritis seen in scarlet fever is of toxic origin and is not a manifestation of rheumatism.

**Suppurative arthritis** is a rare complication of scarlet fever. Three cases occurred in this series of 5549 cases. All were in severe types of the disease and were part of a general sepsis, the blood cultures showing hemolytic streptococci. In

## ARTHRITIS COMPLICATING SCARLET FEVER

Day of illness of scarlet fever on which arthritis developed	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	20	21	22	23	29	31	Total
	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	20	21	22	23	29	31	Total
Number of cases	2	2	6	6	8	14	17	6	10	7	6	2	1	4	1	4	2	2	1	1	3	1	1	99

## AGE GROUP—SEX

Number of cases	2½ years.	3 years.	4 years.	5 years.	6 to 10 years.	11 to 15 years.	16 to 20 years.	21 to 25 years.	26 to 30 years.	31 to 35 years.	36 to 40 years.	Over 40 years.	Total.	Male.	Female.
	1	..	4	6	29	12	8	15	9	9	3	3	99	29	70

## DURATION OF ARTHRITIS

Number of days . . .	1	2	3	4	5	6	7	8	9	10	11	12	13	14	15	16	17	18	19	Not noted.	Total.
	2	16	28	19	11	3	1	3	2	..	2	3	2	1	2	1	..	..	..	3	99

## JOINTS INVOLVED

	Hand.	Wrist.	Elbow.	Shoulder.	Foot.	Ankle.	Knee.	Hip.	Total.
Both.....	17	47	7	13	3	11	24	4	126
Single.....	10	13	6	12	2	6	12	2	63
Total joints.....	44	107	20	38	8	28	60	10	315

(Seven patients with generalized or fleeting pains excluded.)

one case, the left knee joint was involved; in another, the left knee and right wrist joints, and in the third case the metacarpophalangeal joint of the right index finger.

The affected joints are painful, swollen, reddened, hot and tender. The fever is high and the usual symptoms of septicemia are present. Two of these patients received scarlet fever antitoxin early in the disease and all received repeated transfusions. Fortunately, the 3 patients recovered.

In this type of case, scarlet fever antitoxin, convalescent serum, sulfanilamide and transfusions are aids in saving life.

The treatment of the suppurative joint is surgical. Incision and drainage is usually followed by more or less impairment of function of the joint, especially when the knee joint is involved, and requires the services of an orthopedic surgeon.

## CLINIC OF DR. A. V. HARDY

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### ARTHRITIS IN BRUCELLA MELITENSIS INFECTIONS

**Comparative Pathology.**—*Brucella melitensis* infection is primarily a disease of domestic animals. Man becomes involved surprisingly infrequently through the contacts necessary in caring for these animals or through the handling or use of food products from these sources. Though the general clinical manifestations of *Brucella melitensis* infection in man and animals appear to vary widely, the pathologic processes have striking similarities. Orchitis, for example, is a complication common to various animal species and to man, and mastitis which occurs so frequently in cattle is observed occasionally in man. Arthritic manifestations may also be studied in both animals and humans.

There are 3 varieties of *Brucella melitensis*—the *melitensis* (or caprine), the *abortus bovine*, and the *abortus porcine*. These may be readily differentiated culturally, through the bacteriostatic action of certain dyes. Reasonably accurate classification may also be obtained through noted variations in pathogenicity for animals. The *abortus bovine* variety, which but rarely involves animals other than cattle, produces the mildest infection with few complications. The porcine and caprine strains, both of which may also infect cattle, tend to produce severer diseases, though with some variations in pathologic manifestations. All of these varieties are encountered in the United States. The *melitensis* strains are limited largely to the goat-raising areas of the Southwest, the porcine to the hog-raising states of the Middle West, but the bovine is disseminated widely in all parts of the United States.

The frequency of arthritic manifestations parallels the general severity of these infections. In guinea-pigs inoculated with bovine strains complications of this nature are rare. In our own experimental studies with the porcine strain, suppurative arthritis and spondylitis were relatively common. *Melitensis* infections, as described in the literature compare, in this regard, with the disease produced by the porcine varieties.

In natural infections in swine also, arthritis is not uncommon. The joint or joints become swollen, and are obviously painful. In these destructive lesions of bones and joint surfaces are found. In cattle, on the other hand, the joint may become markedly swollen, but evidently without pain. Here bone involvement is lacking and the aspirated fluid is serous. From such lesions *Brucella melitensis* *var.* *abortus* (bovine) has been isolated. It is by no means established, however, that similar arthritic manifestations may not arise from a variety of causes.

***Brucella Arthritis in Man.***—The frequency and nature of arthritis in undulant fever varies widely, dependent on the variety of the organism involved. As in animals so in man, this complication is rather rare in the milder infections caused by the bovine strains. In disease produced by porcine strains such involvements are rather common, but evidently less so than *melitensis* infections observed in the Mediterranean regions. In Iowa where about one third of the infections were of porcine origin, arthralgia was a symptom noted in 36 per cent of the cases, but was a prominent complaint in but 7 per cent of all. Characteristically, multiple joints were involved, with the pain shifting from one joint to another. In order of frequency, those involved were knees, elbows, ankles, shoulders, wrists, fingers and toes. Usually there was no detectable physical abnormality. Only occasionally were the joints swollen, red and very painful. In 1 case we observed, as others have described in the literature, the massive and relatively painless swelling of an hydrarthrosis. These complications usually developed late in the disease and occasionally only in convalescence. Complete subsidence without residual manifestation was the rule.

That an eroding suppurative arthritis is caused by *Brucella* infection of man (as is true of animals) is also well established. The frequency of this is as yet quite undetermined. We have



observed such lesions only in the spine and wrist joints. In clinical character these closely simulated tuberculous involvement and undoubtedly are commonly so diagnosed. A more frequent consideration of *Brucella melitensis* infection is clearly warranted in such cases.

**Diagnosis.**—Of first importance in the diagnosis of all types of *Brucella* infections is a wider appreciation that these organisms are very widely distributed in nature and that man is frequently exposed. If considered seriously, a correct diagnosis of undulant fever and its complications is usually attained. The aid of the laboratory is essential. A normal or low white blood count is of material aid in differentiating from pyogenic infections. A positive serologic test is highly reliable, but in chronic disease a negative finding is not conclusive. Bacteriologic studies, especially of suppurative lesions, are indicated but these are quite unreliable unless the peculiar cultural requirements are appreciated. Skin tests and the opsonophagocytic reaction in the hands of workers, experienced with this infection, are also of some aid.



## CLINIC OF DR. ARTHUR KRIDA

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#### ACUTE SUPPURATIVE ARTHRITIS: RECOGNITION AND TREATMENT

THE orthopedic surgeon, having to deal so often with the consequences of joint suppuration, is led to inquire whether some of the more unfortunate results of such suppurations may not be to a great extent minimized or prevented by, in the first place, early recognition of the seriousness of the disease and in the second place, by more attention to the details of its treatment. The complications of joint suppuration in the order of their importance may be stated as follows: (1) death; (2) chronic suppuration with discharging sinuses and chronic toxemia; (3) bony ankylosis with or without deformity; (4) joint disorganization with painful limitation of motion usually with deformity; (5) temporary stiffness of the joint with gradual recovery of function.

Into which of the above categories the outcome of an individual case will fall will depend in the first place upon the virulence of the infecting agent, in the second place upon the resistance of the individual and in the third place upon the treatment accorded that case.

The early symptoms of acute joint suppuration are fever, pain, swelling of the joint with effusion, limitation of movement of the joint by muscle spasm, and tenderness on pressure about the joint. The effusion is purulent in character and not infrequently will yield the causative organism on culture. As the process develops, the effusion gradually becomes less and is eventually replaced by general infiltration. The average time period for these changes is from three to four weeks in an untreated case. At this time, the joint has been converted into a cavity containing debris and a small amount of exudate, and

the synovial membrane has been converted into inflammatory granulation tissue. The articular cartilages have been invaded and this invasion may have gone on to complete destruction with infection of the underlying bone ends. The abscess may in the meantime burst through the capsule and become evacuated either by incision or spontaneous rupture. A period of chronic suppuration ensues which is accompanied by great pain and toxemia. In such a joint bony ankylosis is apt to be the outcome.

It will be at once apparent that it is important that the grave character of the process be recognized at an early stage, if the joint is to be salvaged.

From a review of numerous case histories of suppurative arthritis, it is striking to note how frequently these cases are considered as rheumatic fever or cases of milder types of infectious arthritis. The manifestations of suppurative arthritis are much more severe than those of most mild types of joint infection. Indeed, the pain is frequently so great that the patient is apprehensive not only about being moved about in bed but apprehensive about the slightest movement of the bed clothes or of the bed. The outstanding aid in the diagnosis is aspiration of the joint and the examination of the exudate.

The importance of joint aspiration can hardly be overestimated. It is a harmless procedure which yields valuable information and is frequently of great therapeutic value as well.

The *x-ray* is unfortunately of no value as an aid in the diagnosis of the early phases of joint suppuration. In the later phases, the *x-ray* is of great value in assessing the amount of joint damage which has taken place. The most striking *x-ray* finding in the intermediate phase of joint suppuration is lessening of the joint space as shown in the film. This is a direct measure of the extent of damage to the articular cartilage and is of great value in the prognosis of the probable outcome of the case. The *x-ray* also is of value in the elucidation of those rather uncommon cases in which joint invasion has been secondary to a focus of osteomyelitis in the neighboring bone.

Treatment of acute joint suppuration should have 3 things in mind: (1) the treatment of the active infection; (2) the "long look ahead" about the attitude of a joint destined to ankylosis, and (3) the treatment of the sequelae.

In dealing with acute joint suppurations the practitioner is apt to place too much emphasis upon the discovery and control of the focus of infection and too little upon the local treatment of the infected joint. This is an eminently proper attitude to adopt in dealing with gonorrheal arthritis but in nearly all other joint infections, valuable time is lost by searching for a remote cause in an infecting focus while the damage is progressing within the joint.

Gonorrheal infection is the exception to this general observation. It has long been recognized that the control of the genito-urinary infection exercises a favorable influence upon the course of the arthritis. The newer methods of treatment by hyperpyrexia have only served to emphasize this older clinical observation.

A purulent exudate within a joint should be evacuated as promptly and as completely as possible. In most cases this can be accomplished by aspiration and lavage through the aspirating needle and this process may be repeated as often as the exudate reaccumulates.

In that minority of cases where aspiration is unsatisfactory or not feasible, the abscess in the joint should be incised and drained.

With reference to incision and drainage of joints, it may be stated that a considerable variation in details of management is discovered in practice. The ideal situation is one in which the joint is opened by one or more incisions, a rubber tissue sutured to but not within the capsule, and motion instituted, as in the Willems method. In actual practice this ideal is probably less often realized than one would hope.

In those severe cases in which, despite drainage, infection progresses, and the knee joint is a typical instance, and it appears that the limb might have to be sacrificed, it is at times wise to open the joint widely by an anterior horseshoe incision, flex it to a right angle and expose all parts of it for drainage and application of antiseptic solution. In such cases, as the infection subsides the joint is gradually straightened and ankylosis allowed to take place in a favorable attitude.

"The long look ahead" may be approached from 2 standpoints: (1) those joints in which recovery with preservation of motion is to be looked for, and (2) those joints in which

bony ankylosis or great limitation of motion is to be anticipated.

1. Those joints in which recovery with motion is to be anticipated should be handled with a judicious mixture of rest and motion. An inflamed joint primarily demands rest but with care and ingenuity a certain increasing amount of motion may be instituted and by this means shorten the convalescence and limit joint stiffness.

2. Joints which by the nature of the infection and the general clinical background are assumed to be destined to ankylosis need fixation by splintage in the most favorable attitude for that particular joint. This is a truism which should not need repetition, but the orthopedic surgeon has so frequently to deal with the results of the neglect of this principle that his point of view may be a little distorted and he may be pardoned for the reiteration.

## CLINIC OF DR. T. LLOYD TYSON

FROM THE DEPARTMENT OF MEDICINE, COLLEGE OF PHYSICIANS AND SURGEONS, COLUMBIA UNIVERSITY, AND THE ARTHRITIS CLINIC OF THE PRESBYTERIAN HOSPITAL\*

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### SPONDYLITIS ANKYLOPOIETICA

THIS disease, perhaps better known as Marie-Strümpell spondylitis or Bechterew's disease, is a primary synovitis of the intervertebral joints, with subsequent calcification of the ligamentous structure and eventual rigidity of the spine. In moderately advanced cases it presents a characteristic clinical and roentgenographic picture which cannot be confused with other ankylosing diseases of the spine.

First described by Marie, Strümpell and Bechterew at the end of the last century, the disease aroused a great deal of interest and controversy because of certain differences in description insisted upon by these authors. Bechterew described the disease as one starting in the cervical region and progressing caudad, while Marie and Strümpell reported initial involvement of the lumbar spine with subsequent extension cephalad. It is now generally agreed that these differences are merely of localization of the disease and that the fundamental process is the same in each.

Spondylitis ankylopoietica, while not common, is encountered much more frequently than is ordinarily supposed. Buckley collected 150 cases in six years. During a five-year period. Anton Fischer reported 98 cases and Erlich reported 260. In the Arthritis Clinic at Presbyterian Hospital 1 case is encountered to about every 13 cases of rheumatoid arthritis. It is primarily a disease of adolescents and young adults, but

\* The Arthritis Clinic of the Presbyterian Hospital is supported by The Faulkner Memorial Fund.

may occur at any age. The average age of onset in Buckley's cases was thirty years. The sex distribution is striking and has been commented upon by all authors. It is predominantly a disease of males and Freund states that he has seen only 1 instance of the disease in a woman. It is generally agreed that it occurs from six to ten times more frequently in men than in women. Not infrequently it affects 2 or more members of the same family. Marie reported a similar disease in cats.

Pathologically the process begins as a synovitis of the small intervertebral joints. This is accompanied by osteoporosis of the vertebral bodies and if the disease begins in the lumbar region, a synovitis of the sacro-iliac joints. In those cases in which the process begins in the cervical and thoracic spine, costovertebral synovitis is an early change. Later, calcification occurs in the longitudinal ligament, the ligamentum flavum and the lateral borders of the intervertebral disks, giving the characteristic bamboo appearance to the spine. Involvement of the intervertebral, costovertebral and sacro-iliac joints frequently gives rise to destruction and ankylosis. Exostoses rarely occur and then only secondarily. It will be seen that this is a totally different picture from that of osteo-arthritis of the spine with osteophyte formation and bridging. According to Elliott, Virchow was the first to differentiate these two great groups of arthritis of the spine; osteo-arthritis, a degenerative process occurring in the aged and spondylitis, an infectious process in the young.

The finding of arthritis elsewhere is common and has been commented upon frequently. Involvement of the pelvic and shoulder girdles is particularly apt to occur and led Marie to call the disease "*spondylose rhizomélisque*." The smaller joints of the extremities are also occasionally involved, presenting the typical changes of rheumatoid arthritis. In these cases the process invades the joints in a centrifugal order, beginning at the root joints and extending peripherally. In Fischer's series 29 per cent had such involvement. Because of this and the fact that so many of these patients have a past history of acute rheumatic fever or other evidence of rheumatism, the majority of clinicians believe that spondylitis ankylopoietica is simply rheumatoid arthritis of the spine and its cause the same as that



of rheumatoid arthritis elsewhere. Hench and Bauer in a recent review of the literature voice this opinion and our experience at the Arthritis Clinic of Presbyterian Hospital is confirmatory. There are, however, many who believe Marie-Strümpell spondylitis may be the result of many etiologic factors, among them typhoid, gonorrhea, rheumatoid arthritis, trauma and various infections. There is one significant fact that seemingly supports this concept, namely, the sex incidence. If spondylitis ankylopoietica is purely rheumatoid arthritis of the spine why should it occur so predominantly in males, while rheumatoid arthritis occurs three times more frequently in females? When we search clinical experience, however, we find a similar discrepancy in sex distribution in the manifestations of another disease. This comparable situation exists in the case of chronic alcoholism and the Korsakoff syndrome. In both conditions the etiology is alcohol, but according to Draper, Korsakoff's syndrome is seven times more prevalent in females even though alcoholism is six times more frequent in males.

Our experience at the Presbyterian Hospital has definitely indicated that the incidence of neisserian infection in patients with spondylitis ankylopoietica is no higher than its occurrence in patients with other diseases. When it does occur there has been no apparent relationship between the two. It would seem probable that the cause of spondylitis ankylopoietica is an unknown infectious process as in rheumatoid arthritis and that the same factors, undue fatigue, focal infections—especially with the hemolytic streptococcus—debility and familial history of rheumatism frequently pave the way to the establishment of both diseases.

The roentgenologic features of Marie-Strümpell spondylitis are characteristic and, in the more advanced stages, pathognomonic. Here, too, one finds a similarity to rheumatoid arthritis. As pointed out by Taylor *et al.*, the roentgenologic changes are similar to those noted in cases of rheumatoid arthritis, except for the anatomic distribution. The earliest change is general decalcification, followed by haziness in the intervertebral joints of the spine. Oblique films are often necessary to demonstrate this. In well over 90 per cent of cases a definite early x-ray finding is obliteration of the sacroiliac joints and this testimony, together with general osteo-

porosis, should make one suspect the diagnosis. As the disease advances osteoporosis with coarse trabeculation becomes more

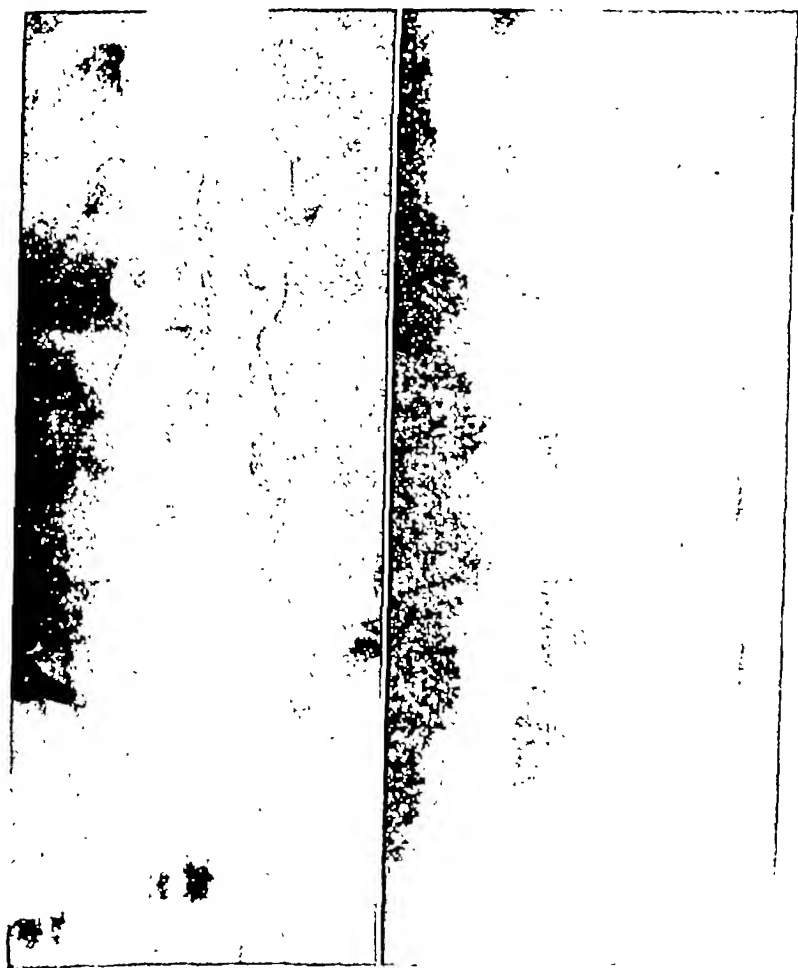


Fig. 126

Fig. 127

Fig 126 —An advanced case, showing calcification of ligaments with the characteristic bamboo appearance

Fig 127 —A lateral view of Fig 126

marked and calcification of the ligaments of the spine and of the outer borders of the intervertebral disks occurs. Finally the intervertebral and costovertebral joints becomes ankylosed

and the spine then becomes one continuous rigid unit (Figs. 126, 127). In only the very advanced cases, however, is the whole spine involved. Usually the process limits itself to one or another section.

The clinical signs and symptoms are variable, depending upon the acuteness of the onset and the localization of the process. In the majority of cases the onset is insidious, but in about 10 per cent it is acute.

In the acute form the symptoms may come on abruptly with fever, leukocytosis, high sedimentation rate and agonizing pain. The pain is due to actual involvement of the nerve trunks by the inflammatory process as well as synovitis of the joints of the spine. It is usual to find root pains as well as back pain. Sciatic pain is a common occurrence and was present in about 40 per cent of Krebs' cases. If the lower dorsal roots are involved the pain may be indistinguishable from that of renal colic or an acute abdomen. Areas of hyperesthesia frequently may be demonstrated and pressure or tapping over the spinous processes causes severe pain. Rigidity of the spine is usual with marked spasm of the paravertebral muscles. Transitory lower motor neurone paralyses also occur and where sciatic pain is severe the Kernig sign may be positive. Due to involvement of the costovertebral joints there occurs in some instances severe respiratory pain which may simulate pleurisy.

In such cases the disease may run its course in a few months leaving the patient with a completely ankylosed "poker" spine and marked wasting of the musculature; or it may assume a subacute or chronic form. This type of onset is more apt to occur in the young and occasionally is complicated by typical mitral stenosis, a finding which favors the opinion that spondylitis ankylopoietica, like rheumatoid arthritis, is related to rheumatic fever.

Far more frequently the onset is insidious with fleeting, variable pains and increasing stiffness of the spine. Frequently during the early stages such diagnoses as lumbago, neuralgia or sciatica are made until time makes the correct diagnosis evident. With advancing activity of the disease the patients lose weight, sometimes as much as 30 or 40 pounds in a year, the stiffness becomes more marked and thoracic respiration gradu-

ally becomes lost. It is then the patient develops the characteristic carriage and movements which make it possible to diagnose his condition from a distance.

Fixation of the spine invariably occurs in the position the patient habitually assumes. If the onset and course are acute and the patient in bed, the resulting ankylosis is straight. In ambulatory patients fusion is most apt to take place with the development of a well-marked dorsal kyphosis and loss of the normal lumbar lordosis. Despite the extreme degree of pain and crippling which this form of arthritis leads to, the prognosis is not as bad as one might expect. Death from the disease is a rare occurrence and somehow, these patients make an adjustment to their disability and frequently live to old age.

The treatment of the disease is the same as that of rheumatoid arthritis and may be divided into general and specific measures. As the disease is a general debilitating infection general measures should include adequate rest and attempts to build up the individual's general resistance. A high vitamin, high caloric diet, large doses of cod liver oil, iron, removal of foci of infection, and salicylates for pain are the most beneficial measures. Transfusions are frequently valuable even when the anemia may be only moderate. Vaccines, gold salts and hyperthermia, while recommended by some, have been, in our experience, rather disappointing. The specific measures are orthopedic in nature and are most important to prevent deformities. A stiff spine in good position is not a severe handicap and can be attained in most cases where the diagnosis is made early. To accomplish this, patients should be fitted with a spinal brace to be worn during the day and instructed to sleep on the back at night. A board should be placed between the mattress and spring and no pillow used. Deep breathing exercises should be taken often to prevent the loss of thoracic respiration. Surgery, such as spinal fusion, is contraindicated.

Finally, it should be emphasized that any patients complaining of generalized pain, especially in the back, shoulders or sciatic region, with an elevated sedimentation rate, should be suspected of having Marie-Strümpell spondylitis and should have roentgenologic study to confirm or rule out this diagnosis.

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## CLINIC OF DR. LEWIS CLARK WAGNER

### HOSPITAL FOR THE RUPTURED AND CRIPPLED

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#### CHRONIC BONE ABSCESES (BRODIE) SIMULATING SYMPTOMS OF ARTHRITIS

**Introduction.**—Arthralgia is most likely to be associated with intra-articular pathology which may be transitory or dependent on more permanent changes which produce alterations in the periarticular structures, synovial membrane, and articular cartilages. Arthralgia caused by definite extra-articular pathology is rare, and can only be through sympathetic reactions in the adjoining structures. Chronic metaphyseal bone abscess may be the hidden cause at times for such symptoms.

In 1842, Sir Benjamin Brodie described certain findings which today are quite a common occurrence. It might be pertinent to quote his words: "Chronic inflammation, producing a chronic enlargement of the epiphysis, is a not infrequent occurrence, and is liable to be mistaken for disease in the joint itself; the more so, as inflammation of the synovial membrane sometimes occurs as a secondary disease. Occasionally, chronic inflammation of an epiphysis terminates in the formation of an abscess in the center of the bone, but contiguous to the joint. An abscess of this kind is attended with an extraordinary degree of suffering."

It is interesting to note that occasionally amputation has been resorted to, but we know today the treatment is considerably more simple when the exact pathology is noted.

**Etiology and Pathology.**—The cause of these abscesses is the result of an epiphysitis. Therefore the beginning arises in the younger years of life when the epiphyses are patent. The latent infection becomes active with the resultant localized abscess formation. The condition is always chronic, never acute. These abscesses, because of their chronicity, cause sclerosis in the surrounding bone structure as compared to a

very acute inflammation, such as if induced by virulent pyogenic organisms. One finds acute necrosis rather than any acute abscess formation. Nonvirulent staphylococci are most likely to be responsible. In the first or quiescent stage, there is a cavity filled with serum and lined with a membrane like the periosteum of young bones. When the mature stage of the abscess arises, the lining membrane is converted into granulation tissue and the cavity becomes filled with staphylococcus pus. The outer layer of granulation tissue erodes and the abscess becomes progressively enlarged. As the bone is eroded within, new bone is formed. If pus formation is more rapid than bone erosion, there is tension and pain, but if bone erosion is sufficiently rapid to prevent tension, there is little or no pain. In the final stage, the abscess perforates the bony shell on the periosteal surface or into an adjacent joint.

**Symptoms.**—The symptoms are often difficult to differentiate and are most often thought to be rheumatic in origin. Pain is ever present and can be usually controlled by aspirin. Irregular sweats with occasional fever may be present. The harassing pain causes sleeplessness, exhaustion and, at times, emaciation. There is partial loss of function to the affected joint and occasionally there is an accompanying synovitis. The tenderness is marked even when pain is absent. *The pain is not in the joint as the patient suspects, but is at the site of abscess.*

The following 3 case histories are presented in order to show the symptoms are not unlike arthritis and had been treated as such until pathology was noted.

### RÉSUMÉ OF CASES

**Case I.**—Oscar J., aged twenty-four, admitted to the hospital May 9, 1936

For the past eight years, patient has had pain about the right shoulder and extending to the arm. He has been treated continuously for rheumatism. The pain seemed to be centered in the shoulder joint itself and radiated backward to the scapula. In the beginning, the pain did not trouble him in the daytime and it was noted only in the early morning which would cause him to get up and walk about. He has had a thorough search for foci of infection. Tonsils and teeth have been removed and to date the pain has been continuous. It is necessary for him to take certain amounts of codeine daily.

**Examination** is negative except for the right shoulder. The right shoulder girdle shows moderate atrophy. There is, however, no restriction of motion except in abduction. He does handle the shoulder joint with care. There is



moderate atrophy of the biceps muscle. The bicipital region in the right measures  $10\frac{1}{2}$ , and the left  $11\frac{1}{2}$ . The right forearm measures 9, left  $9\frac{1}{2}$ . There is no tenderness about the scapula or shoulder joint except about the head of the humerus. Posteriorly, there is no tenderness. With the arm in neutral position in the region of the subscapularis muscle close to the axillary plexus, there is some thickening and marked tenderness on palpation.

*x-Rays* of this region (Fig. 128) show a definite rarefaction circumscribed in the medial aspects of the humerus about 1 inch from the shoulder joint. There is considerable calcium laid down on the outer surfaces of this area.

*Diagnosis.*—Chronic bone abscess (Brodie), right upper humerus.



Fig. 128.—A, x-Ray showing area of rarefaction in head of humerus prior to operation B and C, x-Ray postoperative, showing cavity filled in with new bone.

*Operation.*—The right humerus was explored. A small window was made in the medial and anterior surface of the humerus and the abscess cavity located. It was filled with a gelatinous reddish-looking material which was curetted out. All rough edges were removed and the wound closed without drainage. Patient made an uneventful recovery from operation and volunteered the information the following morning that his old pain was gone. x-Rays taken two years later show the cavity to have filled in with new bone, and the patient is symptom free.

*Comment.*—Analysis of the above pain findings could lead one to suspect a brachial plexus syndrome, either by pressure

or inflammation of the nerve roots. The tenderness and atrophy of the arm and the slight restriction of motion lead one to suspect arthritis. The true cause of pain was noted only by the x-ray findings.

*Case II.*—Russel DeS., aged twenty-four, admitted to the hospital December 10, 1934.

Patient is a British West Indian, who for the past five years has had pain in the left hip joint region. Pain at times radiated to the hip and ankle and



Fig. 129.—Preoperative x-ray shows area of necrosis about lesser trochanter of femur

he had considerable difficulty in walking. He had some restriction of motion, especially external rotation of the hip. Pain had been intermittent in character and was partially controlled by aspirin. For the past ten months, pain has been almost unbearable. He has consulted a great many physicians and x-rays were taken and called negative.

*Examination* reveals patient to be in splendid physical condition. There is no evidence of polyarthritis about the terminal joints. Examination is concentrated on the left lower extremity. There is moderate atrophy of the left thigh and patient walks with a left limp. There is restriction of external rotation and extension of the left thigh. There is some tenderness on deep palpation in the region of the lesser trochanter. Forced movements give the patient

pain. A thorough laboratory examination reveals blood count, blood chemistry and urine within normal limits. Spinal fluid, normal pressure, protein 27, and manometric examination normal.

*x-Ray* of the entire body showed nothing unusual except in the region of the lesser trochanter of the left femur (Fig. 129) about 1 inch from the hip joint, a definite rarefaction at the base of the lesser trochanter, measuring about 1 cm. in width with sclerotic changes in the surrounding bone was noted.

*Diagnosis.*—Chronic bone abscess (Brodie), left femur.

*Operation.*—The following morning, the left hip joint region was explored through an anterior incision. Definite sclerotic changes were noted in the periosteum about 1 inch above the lesser trochanter. A window was made in the bone in this region and an abscess cavity was encountered. The cavity was filled with a seropurulent material and considerable semisolid drainage. Cultures from the wound were negative and microscopic examination of the fragments of bone and granulation tissue revealed necrotic bone and chronic inflammation. Patient was examined two years later and has complained of no further pain. Normal motion has been restored to the hip joint and he has gained about 20 pounds in weight.

*Comment.*—Analysis of the above pain findings leads one to suspect a sciatic syndrome, the pain in the hip being caused by an inflammation of the lumbosacral roots, as there was only slight limitation of motion in the hip and the tenderness of the hip joint could not be noted because of overlying musculature. The diagnosis of arthritis was suspected. Because the patient took aspirin continuously, drug addiction was considered and only by *x-ray* study was the nature of the lesion discovered.

Case III.—Rupert Z., aged thirty-four, admitted to the hospital June 30, 1930.

For fourteen years he has had swelling in the region of the internal malleolus. It has been associated with attacks of pain from time to time which laid him up for one or two days. The pain at times has almost been unbearable and his treatment has always been for arthritis. Tonsils have been removed. His gastro-intestinal tract has been explored. Many teeth have been removed without any improvement. Six weeks prior to admission to the hospital, he had had a very severe attack of increased pain, swelling and heat around the ankle and was unable to continue with his work. Examination at that time showed patient to be in good condition and in considerable pain.

Examination was negative except for the right lower leg. There was considerable thickening and swelling about the ankle joint. The greatest edema seemed to be around the internal malleolus. Motions of the joint were markedly limited. He had no temperature.

*x-Ray* showed a definite rarefaction in the lower end of the tibia (Fig. 130). There was marked periosteal thickening. This rarefaction measured about 1 X

1½ cm. The abscess cavity was very close to, if not communicating with, the ankle joint.

*Diagnosis.*—Chronic bone abscess (Brodie), lower end of the tibia.

*Operation.*—The following morning, the internal malleolus was explored through a longitudinal incision. There was moderate thickening about the periosteum. A small window was made in the tibia and the abscess cavity entered. Definite seropurulent material exuded and on culture revealed *Staphylococcus albus*. The wound was thoroughly curetted. All loose bone removed and, because of the acute inflammation at the time, the wound was drained.

*Reexamination* in April, 1937, seven years after operation, revealed that the patient has been pain free, with normal motions in the ankle. Swelling



Fig. 130.—A, Preoperative x-ray showing cavity with necrosis in internal malleolus and lower end of tibia. B and C, x-Ray (postoperative seven years) showing cavity filled with new bone

has disappeared and to date both ankles measure the same in circumference. There is no disturbance of motion in the ankle joint and x-ray shows consolidation of the bony cavity.

*Comment.*—Analysis of the above findings leads one to think only of chronic monarticular infectious arthritis with acute exacerbations. It is strange that patient suffered eighteen years (three years in war duty) and no physician suggested x-ray by which the diagnosis was made.

*Diagnosis.*—The diagnosis of these chronic abscesses is at times most difficult, but one should hold in mind the ever-present possibility. Extensive x-ray studies of the bones in

various positions should be made. One can often overlook the pathology in overexposed films and x-rays taken for bone detail are always indicated. On several occasions, I suspected an abscess, but it could not be demonstrated by x-ray until many films had been taken. The constitutional symptoms are few, if any, except a loss of weight, and this fact is only noted because, after operation, the patient seems to gain weight in every case. The abscess usually occurs near the upper margin of the metaphysis of the bone. One can find localized tenderness on pressure and percussion, hydrops of the adjacent joint, local enlargement of bone and superficial veins. The persistence of "boring" pain, referred to a joint and center of affected bone, atrophy of the extremity, slight limitation of motion in certain directions, the control of pain by aspirin, can lead one to suspect the presence of a chronic bone abscess.

**Treatment.**—Once the diagnosis made, the treatment indicated is surgical drainage. The cavity is explored through a small opening in the bone and the bone cavity is evacuated of its serum, seropus, or gelatinous reddish granulation tissue. The edges of the cavity are thoroughly curetted and all rough edges smoothed off. As the contents of the cavity are sterile in most instances, the wounds are closed without drainage. No further treatment is indicated. The relief of pain is spectacular and, when operation has been accurately done, there is no recurrence.



## CLINIC OF DR. ALAN DEF. SMITH

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### DIFFERENTIAL DIAGNOSIS OF CONDITIONS CAUSING PAIN IN THE LOWER BACK

Case I.—The patient is a young man of twenty-two whose complaint is pain in the lower back. His first recollection of this symptom is that he had



FIG 131.—Case I. Lateral x-ray of the lumbosacral region, showing posterior displacement of the fifth lumbar vertebra on the sacrum.

a severe pain nine years ago after wrenching his back, at which time he was in bed for two weeks. There was no recurrence until four years ago, when

again he strained his back by lifting a heavy weight. This caused him to go to bed for one week. Since then he has had intermittent attacks of pain, some of them very severe, precipitated by bending forward, lifting heavy weights or doing any kind of hard work. His back feels weak and is easily fatigued. He was seen for the first time in the clinic in December, 1934. *x*-Rays were taken of the lumbosacral region, which revealed anteroposterior articulations between the fifth lumbar and first sacral vertebrae and a posterior displacement of the fifth lumbar on the sacrum. He was provided with a belt and exercises were prescribed. These had little effect in relieving his pain, which has continued and has been getting progressively worse. A spine fusion of the fifth lumbar vertebra to the sacrum was advised and he has been admitted to the hospital for this procedure.

We see a stocky, healthy appearing young man with good muscular development. Physical examination shows nothing of importance except in the lumbosacral region. He stands without deviation of his trunk to either side, but tends to list over toward the right when he bends forward. There is no limitation of motion in the lumbar spine. Motion is equally free in the sitting position. We now have him lie prone on the examining table. There is localized tenderness over the spinous process of the fifth lumbar vertebra and the ligament between this and the first sacral spine, but none over the sacro-iliac joints or the lumbar or gluteal muscles. Flexion of the knees with the hips extended is not limited. Compression of the iliac crest causes no pain and there is no pain from hyperextension of either thigh with the opposite hip fully flexed. (This is called the Gaenslen sign and is a test for sacro-iliac arthritis.) Flexion of the hips with the knees extended is neither limited nor painful.

A lumbar puncture was done and it was found that the spinal fluid was clear and under normal pressure. No cells were found in the fluid and the total protein content was 20 mg. per 100 cc. Spinal punctures are now done as a routine on all patients who are to be operated on for low back pain, in order to eliminate cases of spinal cord tumor or other lesions within the spinal canal.

This case is typical of a back which is structurally weak because of the nature of the development of the lumbosacral joint and which is incapable of withstanding the stresses to which it normally is subjected. With such a history of long repeated attacks of pain and failure of conservative treatment to relieve the condition, spine fusion is indicated and is the only means that we have of effecting a cure.

Several factors combine to make the lumbosacral junction a weak area in *Homo sapiens*. In the first place, he has not yet become completely adjusted to the upright posture and the change in stresses which this has brought about. The lumbosacral joint is at the junction of the anterior lumbar and the posterior sacral curves, and of the movable with the fixed por-



tion of the spine. The structure of this part of the skeleton has not become sufficiently stable in pattern to be uniform, and there are numerous developmental variations, many of which tend to detract from the strength of the joint. Among them are the following:

The lumbosacral angle, which is the inclination of the superior surface of the sacrum from the horizontal, is normally about 42 degrees. When it exceeds that figure, or in other words, when the upper surface of the sacrum approaches more nearly the vertical plane, the shearing strain, which tends to make the fifth lumbar vertebra slide forward on the sacrum, is increased, and this often results in pain.

The direction in which the facets of the lateral articulations face is of great importance, and varies considerably at this level. The normal internal-external or sagittal type of lumbar joint enhances stability. When these articulations are anteroposterior, or coronal, they are much less stable and are vulnerable to injury. Asymmetrical articulations are particularly liable to result in low back pain.

Posterior displacement of the fifth lumbar vertebra on the sacrum, although usually of only slight degree, is common and a very frequent cause of low back pain. Because with this displacement the canals through which the fifth lumbar nerve roots emerge from the spine are made smaller, sciatica often results from pressure on these roots.

A forward displacement of the fifth lumbar vertebra, or spondylolisthesis, also occurs frequently, but not as much so as the posterior one. It is caused by a congenital defect or failure of union in the laminae of the fifth lumbar vertebra, usually between the upper and lower lateral articulations. The condition usually causes pain, although often not until adult life.

Because an evolutionary trend is active in the lumbosacral area, producing a shortening of the trunk by the migration of the pelvis upward, we find many individuals who have transitional lumbosacral vertebrae which have some of the characteristics both of lumbar and sacral vertebrae and which give rise to mechanically unstable joints.

Lesions of the intervertebral disk between the fourth and fifth lumbar and first sacral joints may cause a protrusion of the cartilage into the canal with resulting pressure on the cauda

equina and nerve roots, or may so upset the normal mechanics of the lumbosacral joint as to cause strain and traumatic arthritis.

These are some of the more common structural variations in this region which must be looked for in searching for the cause of low back pain. Needless to say, good *x*-rays are essential and must include both lateral and anteroposterior views.

**Case II.**—D. G., a man, thirty-five years old, began to have pain in the lower part of his back one year ago. It was intermittent and not severe. Three months later pain started in his right buttock, back of the right thigh, and outer side of the right leg. This became increasingly severe and for two weeks prior to his admission he had to remain in bed.

He is a tall man with well-developed muscles. All movements of his back are very limited and painful and he can stand only with great difficulty. There is marked spasm of the sacrospinalis muscles and his trunk lists to the left side. Tenderness is marked over the right sacro-iliac joint and gluteal muscles. The patient is placed on his left side and the left hip and knee are flexed sufficiently to obliterate the lumbar lordosis. The right leg is then grasped just below the knee and the thigh is abducted and extended while the pelvis is steadied by the left hand. The right lower extremity is then allowed to drop toward the table as far as it will, care being taken not to allow the hip to rotate externally. In this case the thigh remains in abduction and the maneuver increases the patient's pain. He then is turned over on his right side and the test is repeated with the same result, except that it causes pain on the right, or opposite, side to the one being tested.

This test is the one described by Ober to demonstrate contracture of the fascia lata. Ober discovered the existence of this condition in a case of sciatica and complete cure followed the division of the contracted fascia above the trochanter. Since then several hundred patients have been operated on for this condition with good or excellent results in from 75 to 80 per cent. The operation is simple and effective in properly selected cases. Care must be taken to exclude arthritis of the spine, tumors of the spinal cord or abnormalities of the spine. This means a complete set of *x*-rays of the lumbosacral region, a careful neurologic examination, and lumbar puncture in all cases.

By these tests all other conditions have been eliminated in this patient. His diagnosis, therefore, is sciatica due to con-

traction of the fascia lata. Division of the tight fascia will be done with excellent prospects of relieving his pain in this way.

**Case III.**—We have here a woman, forty years old, who formerly was employed as a stewardess on a steamer. Two years ago she began to have pain in the lower part of her back. She does not remember the onset definitely and can recall no injury. The pain increased in severity for several months until she was obliged to stop work. It was confined to the lower part of her back and did not radiate into her thighs. In September, 1935, she applied for



Fig. 132.—Case III. A 45 degree anteroposterior view of the lumbosacral joint. The last lumbar vertebra is transitional and is sacralized on one side.

treatment at the out-patient department of the New York Orthopedic Dispensary and Hospital.

She was a fairly well-developed woman, whose tonsils had been removed and whose teeth were in good repair. Her posture was fairly good. Motion was somewhat limited in all directions in the lumbar spine, apparently because of spasm of the muscles. There was tenderness over the lumbosacral but none over the sacro-iliac joints. Other tests were negative. x-Rays showed a transitional lumbosacral vertebra with incomplete sacralization on the right side. It was thought that this was the underlying cause of her back pain.

A corset, massage and exercises were prescribed and she was told that if her pain persisted after several months of this treatment, a lumbosacral spine

fusion would be advisable. At the end of three months she began to complain of pain in her fingers and left shoulder. There was tenderness over the lateral aspect of the shoulder and abduction and rotation were limited. There were slight swelling and stiffness of the proximal phalangeal joints of the fingers. From this it was apparent that she had a rheumatoid arthritis. Under appropriate treatment the symptoms in the joints improved and the pain in her back almost entirely disappeared.

This case is presented in order to emphasize the importance of considering arthritis as a cause of low back pain and also to show how difficult it may be, in early cases, to differentiate arthritis from some mechanical condition capable of producing the same symptoms. Here the appearance of the symptoms in other joints gave the clue. A careful search for foci of infection should be made in all cases and the history should include an interrogation about other symptoms indicative of arthritis. In doubtful cases a determination of the sedimentation rate may be helpful.

## CLINIC OF DR. LEO MAYER

### HOSPITAL FOR JOINT DISEASES

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#### SCIATICA

SCIATICA is a somewhat vague term used to indicate pain associated with the distribution of the sciatic nerve. It is distinguished from sciatic neuritis in which actual organic changes in the nerve structure occur with consequent sensory and motor changes. These are absent in sciatica. Spinal cord tumors, herniations of the nucleus pulposus, bony irregularities of the vertebrae, may produce pressure against nerves composing the sciatic plexus and thus give rise to pain similar to that of sciatica, but these conditions are accompanied in almost all instances by objective neurologic phenomena such as changes in the reflexes and sensory disturbances. It is therefore important in any case of nerve pain referred to the sciatic distribution, to rule out neuritis, spinal cord tumors, and other extraneous causes of pressure against or irritation of the nerves of the sciatic plexus.

The term "sciatica," like its twin lumbago, has in the past been used as a cloak for ignorance. If the term is to be retained in good medical usage, and it is always difficult to drop a time-honored word, it should be used only in the same general way as the expressions headache or precordial pain, to indicate the distribution of pain and not as an exact diagnosis. For diagnostic purposes the term "sciatica" should be thrown into the limbo of discarded antiquities.

Sciatica is almost always due to a pathologic process in the sacro-iliac or lumbosacral joints and their associated ligaments. This process may be traumatic as in sprains of the ligaments and subluxations of the joints, or infectious as in arthritis, tuberculosis or actinomycosis, or metabolic as in gout. Rarely it may be neoplastic as in chordoma of the sacrum, sarcomata or metastatic carcinomata.

In reaching a diagnosis stress must be laid on an accurate history with particular reference to minor traumata such as strains occurring in putting on the shoes, getting out of bed or lifting a suitcase. In my own practice the larger percentage of cases are associated with an initial trauma. In eliciting a history, care should be taken to locate the distribution of the pain with accuracy. .

Although there is some difference of opinion between neurologists regarding the relationship between spinal segments and the sensory nerve supply of specific skin areas, there is in the main this agreement, that the anterior branches of the first, second and third lumbar nerves supply the anterior portion of the thigh; that the anterior branches of the fourth and fifth lumbar supply the anterior portion of the calf extending down to the big toe on the inner side of the foot; that the anterior branches of the first sacral supply the outer portion of the calf and the outer portion of the foot; that the anterior branch of the second sacral supplies the posterior portion of the thigh and calf. The posterior branches of the second, third and fourth lumbar, first and second sacral supply the region of the buttocks. Just why painful sensations should be felt in the leg without direct involvement of the nerves to these parts is still a subject for debate. It would seem probable that Head's explanation with regard to pain, holds true for the sciatic nerve distribution as well as for the visceral organs. Head states that when there is an irritation of a part of the body less richly supplied with sensory nerves than a corresponding skin area, irritations in the part of lower sensitivity are registered in that portion of the body with greater nerve sensitivity. In other words, if there is an inflammation of the ligaments of the sacroiliac joint normally supplied by a posterior branch of the second sacral nerve, the painful stimulus is felt chiefly in that portion of the buttock which is also supplied by the second sacral nerve. This theory is supported by the fact that in suitable cases of sciatica, injection of the strained ligaments with novocain causes the pain in the sciatic nerve distribution to disappear.

Since the pathologic process is usually in the lower back, the examination should be made so as to locate the exact site of the lesion. The following tests are of particular value:

1. Inspection of the patient in the standing position with the heels placed against a ruler, with the knees straight and the body relaxed. In a large number of patients a tilting of the body toward one side or the other will be noted, accompanied by a scoliosis, usually termed "sciatic scoliosis," and by a torsion either of the pelvis or the lumbar spine, or of the shoulder girdle, or all three portions of the body. Notation should be made of these variations from the normal. The patient is then asked to bend forward and limitations of the spinal motions noted together with the areas of pain which this act induces. Lateral bending and backward bending should also be performed with reference to the limitations of these motions and the pain induced by them. Bending tests should be made with the patient in the seated position, since frequently in cases of sacro-iliac strain, bending is decidedly freer when the hamstring group of muscles are relaxed by the seated position.

2. Palpation for areas of tenderness. Of particular importance are: (a) the sacro-iliac ligaments just below the posterior superior spine; (b) the sacrotuberous ligaments running from the sacrum down toward the tuberosity of the ischium; (c) the lumbosacral joints located about 1 inch from the midline in the angle between the ilium and the sacrum; (d) the points of emergence of the superior gluteal nerve just above the piriformis muscle lying between it and the superior margin of the sacrosciatic notch; (e) the crest of the ilium where the erector spinae muscles and the fascia of the back have their bony attachments; (f) the emergence of the sciatic nerve itself.

3. The straight leg-raising test known as the Lasègue phenomenon. In almost all instances of sciatica this test is positive. It is performed by gently flexing the thigh on the body with the knee completely extended. Normally the thigh can be flexed to an angle of 90 degrees. In a positive test this angle is decidedly nearer 180 degrees. Comparison of the two sides is of use in doubtful cases.

4. Gaenslen test. This is of especial value in determining whether there is any strain of the sacro-iliac ligaments. With the patient lying on the examining couch so that one buttock projects over the edge of the table, the thigh of this side is hyperextended while the opposite side is sharply flexed on the abdomen. This produces a torsion motion of the pelvis and

elicits pain in the hyperextended side of the pelvis if there is an involvement of that sacro-iliac joint. The test is repeated with the patient lying in the reverse direction.

5. The Ober test. This has recently been described by Dr. Ober and its significance is still of considerable debate. The patient is placed lying on his side, the thigh of the corresponding side is flexed to the maximum, the other thigh is then brought into complete extension, the ankle of this extended leg is supported by the examiner. In normal patients, the knee of this side will then drop toward the examining table. In a positive Ober test the thigh remains horizontal or in a position of slight abduction indicating a contracture of the fascia lata holding the thigh in an abducted position.

*x*-Ray examination should always be made. The following views are of value:

1. An *x*-ray picture of the pelvis and lumbar spine with the patient standing. The tube should be centered accurately on the symphysis pubis. This view will illustrate accurately deviations of the sacrum from the vertical position and accompanying scolioses. It will also show any abnormalities of the lumbosacral joints.

2. Lateral *x*-ray of the patient standing to indicate the relationship between the fifth lumbar and the sacrum with particular reference to slight displacements as well as to the occurrence of spondylolisthesis or forward slipping of the fifth lumbar on the sacrum or of the fourth lumbar on the fifth.

3. For accurate study of the joints, pictures should be taken in the recumbent position, not only in the anteroposterior and lateral views but also in the right and left oblique positions. The latter are of particular value in detecting fractures of the articular facets and arthritic changes in the intervertebral joints.

**Treatment.**—The treatment of sciatica must be directed to its cause. For this reason exact diagnosis of the pathologic lesion responsible for the sciatica is necessary for its rational treatment. In general, the treatment falls into two main groups: first, that directed toward the general disease responsible for the sciatica; second, treatment directed to the local cause. In the first group belong the cases of arthritis involving the lower lumbar vertebrae, the lumbosacral joints or the sacro-



iliac joints. Such cases require the same antiarthritic treatment as arthritis of the hip or knee. As in the case of the knee and hip, search must be made for foci of infection which in many instances are found in the gastro-intestinal tract rather than in diseased tonsils or apical abscess of the teeth. In addition to the general antiarthritic treatment, support must be given to the affected vertebrae. In mild cases this can be done either by a well-fitted corset, a spinal brace of the Knight type, or Goldthwait design, or by a plaster-of-paris support. In the more severe cases, the patients require rest in bed, preferably on a frame or in a plaster-of-paris shell.

The second large group of cases is the traumatic. In these the more precise the diagnosis, the more effective the treatment is likely to be. Particular credit should be given to Pitkin, of San Francisco, for his study of the sublaxations of the sacro-iliac and lumbosacral joints and for the methods of reduction which he employs to restore normal relationship. Pitkin has analyzed 1000 cases of traumatic low back pain associated with sciatica and has shown that in the majority, the type of lesion can be determined by exact analysis of the scoliosis and pelvic torsion. He has drawn diagrams illustrating the various patterns which may occur in a flexion or extension displacement of the sacrum on the ilium, in a forward or posterior displacement of the fifth lumbar on the sacrum. By reference to his charts, an accurate diagnosis can frequently be made. The maneuver which he has found most frequently successful to reduce these sublaxations consists in a forward rotation of the pelvis on the trunk combined with an upward push against the shoulder and a downward push against the pelvis. Naturally the rotation should be performed in such a direction as to overcome the particular sublaxation which is dealt with. Pitkin, as a rule, uses no anesthetic and applies only very gentle force. In cases associated with great pain he gives a low spinal anesthesia.

Until the Pitkin publications I had been accustomed to use more vigorous methods of manipulation. Those which have proved of particular value have been, first, the straight leg-knee extended, the thigh is forcibly flexed on the abdomen. Second, the external rotation abduction maneuver. In this the

thigh of the recumbent patient is abducted to 90 degrees, externally rotated and with the fist placed beneath the sacrum, the thigh is forced posteriorly thus tending to leverage the ilium into a forward position.

Third, the hyperextension maneuver. The patient is placed in the prone position, the thighs are hyperextended and as this is done, the sacrum is pressed forward. This maneuver tends to bring the ilium into a posterior position just as the preceding tended to bring it forward. Not infrequently the operator is compelled to attempt all of these maneuvers before he is able to overcome the displacement.

Following the reduction, firm adhesive plaster support should be applied to the lower back. By painting the skin with a solution of mastix or better still with "adherent" of Roth, irritation can usually be avoided. The adhesive straps should be 3 inches wide, and should run transversely from the level of the trochanters up to the first lumbar. Additional immobilization can be gained by including the lower abdomen in the strapping.

In severe cases the patient should be placed in bed. This phase of treatment cannot be stressed too strongly. Of all the measures used for sciatica, none is so important as rest on a firm mattress. If the spring of the bed sags, it is advisable to place boards between it and the mattress.

Physiotherapy has a place but should not be made into a fetish. To place the full responsibility for treatment of sciatica on the physiotherapist, however competent he may be, should be strongly condemned. Diathermy, sinusoidal stimulation, short-wave treatment, infra-red radiation, hot stupes, and gentle massage are all of value if given intelligently.

If analysis indicates that there is no subluxation but simply a strain of the ligaments, manipulation is contraindicated. In both groups when the strapping is removed, a support should be given which will reinforce the sacro-iliac and lumbosacral ligaments. In most cases a belt which gets its grip below the anterior superior spine of the ilium, is sufficient protection. If there is a strain of the lower lumbar spine, a more rigid type of apparatus is required. The Knight spinal brace is frequently effective; of particular value is the brace designed by Dr. Williams of Dallas, Texas. This ingenious device tends to hold

the lumbar spine in flexion thus taking the strain off of the lower lumbar spine and the lower sacro-iliac ligaments.

If, despite successful reduction of subluxations, rest in bed and effective support, sciatica persists, recourse must be had to extradural injections into the sacral canal. This procedure ought in my opinion always be performed in a hospital, not in the office or the home. The patient is placed in the prone position with the hips flexed. By careful observation the site of the sacral foramen just above the sacrococcygeal junction is determined. A few drops of novocain are infiltrated into this region, then with the spinal puncture needle the sacral canal is entered. Twenty-five cc. of 1 per cent novocain solution is injected and then 50 to 75 cc. of sterile saline solution. The injection must be done slowly. In successful cases the fluid should remain within the sacral canal, there should be no external swelling. Cadaver experiments show that fluid thus injected passes upward and outward along the roots of the lumbar and sacral plexus, infiltrating the nerves in this region.

In 1935 Ober, of Boston, published an operative procedure for the relief of sciatica. This consists in the division of the fascia lata in a line extending from the anterior superior spine to the tip of the greater trochanter. The rationale of this procedure has thus far not been discovered but in suitable cases the operation has caused complete relief of sciatic nerve pain. One of the difficulties in carrying out the Ober method is to determine in advance which cases are likely to react favorably.

Sometimes the Ober operation has a transient beneficial effect but the pain returns when the patients resume the upright position. This indicates the need for further analysis of the cause of the sciatica.

In those patients in whom, despite adhesive plaster support or other forms of bracing, the ligaments are so loose as to cause frequent recurrence of sciatica, operative measures must be used to fix the unstable joints. These fusion procedures are necessary in only a small proportion of the cases; in my own experience, in less than 5 per cent. The nature of the fusion depends upon the pathology. If the lesion is situated at the lumbosacral joint, the fourth and fifth lumbar should be fused to the sacrum. If one or both sacro-iliac joints are involved,

these joints should be fused. The technical details of the operation cannot be considered in this article.

**Prognosis.**—Despite inherent difficulties the great majority of cases of sciatica are curable. The incurable cases are those caused by malignant neoplasms, unusually severe arthritis or long-standing displacements associated with compensation neuroses.

## CLINIC OF DR. T. CAMPBELL THOMPSON

### HOSPITAL FOR THE RUPTURED AND CRIPPLED

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#### THE MANAGEMENT OF THE PAINFUL FOOT IN ARTHRITIS

THE complicated structure and the severe duties of the human foot render it peculiarly susceptible to anatomic, physiologic, and pathologic disorders. Only the vital organs have more constant or more difficult functions. Even a normal foot may give way if subjected to weight and strain disproportionate to its resistance, and a foot that is the site of localized arthritic manifestations, either active or quiescent, is rarely normal in structure, appearance, or function. Painful feet are often the chief complaint of the arthritic patient.

**Anatomy and Physiology.**—The study of any foot disorder should be based upon an intimate knowledge of the detailed anatomy of the foot, and a clear understanding of the various strains to which it is subjected in the unconscious effort of the individual to maintain the center of gravity over the weight-bearing area while standing, or to move the body weight forward from one foot to the other while walking. A detailed description of the various bones, ligaments, muscles, nerves, and blood vessels is not necessary here. Neither is it important to describe the arches and their functions, as the actual height of the longitudinal arch is of no importance.

While standing, the foot can be considered a pedestal upon which the body structure is balanced. When walking, it is a lever which acts to move the body weight forward. The weight-bearing area of the foot is roughly triangular in shape and normally the center of gravity of the body is balanced over it with practically no muscular effort. The weight is divided between the tuberosity of the os calcis and the metatarsal heads. The

head of the first metatarsal, through the two sesamoid bones beneath it, bears twice the weight of each of the others. The first and second together should bear as much as the three lateral metatarsal heads. In other words, the center of balance should fall in a line between the second and third toes. In walking, the projection of the center of gravity upon the ground moves forward along a line parallel to the long axis of the foot. This line is practically at right angles to the axis of the ankle joint. From the heel it bends laterally toward the fifth metatarsal head and then turns forward to go between the first and second toes. The weight-bearing area is then enlarged forward by flexion of the toes against the ground as the final "push off" is obtained by the first and second toes. Deformity, loss of flexibility, or pain will upset this entire foot mechanism.

**Foot Pain.**—The great majority of all foot pain can be traced to some anatomic abnormality, incorrect habit, or pathologic lesion which interferes with its normal function. Pain in the arthritic foot can be analyzed into that due to:

1. Localized pressure.
2. Ligamentous or muscular strain.
3. Local inflammation, acute or chronic.

Restoration and maintenance of normal function is usually accompanied by relief of pain.

**Pressure Pain.**—A large number of the common foot ailments can be traced directly or indirectly to excessive pressure. This pressure may be from a smooth shoe against certain irregularities of the foot, or from certain bones of the foot sustaining an undue amount of the body weight. With excessive standing or walking, or when the body weight is disproportionate to the size of the foot, the entire weight-bearing area may become inflamed and painful.

Any foot deformity which alters the shape of the weight-bearing surface, or changes the distribution of the body weight, will cause calluses beneath those bony structures which are thus subjected to excessive pressure. The skin of the foot itself is rarely sensitive, but plantar warts, though a virus infection, are prone to occur in weight-bearing areas and a minute plantar wart may be exquisitely painful. Ordinarily corns occur only at points subject to pressure of a shoe against a bony prominence. A soft corn, which occurs between the toes and

is acutely painful, can usually be traced to pressure of a small exostosis beneath it or upon the neighboring toe.

Calluses beneath any of the bones of the foot indicate poor weight distribution. These are found most commonly beneath the second, third, and fourth metatarsal heads due to spreading of the forefoot.

**Pain Due to Strain.**—Foot strain is probably the most common cause of pain in the feet and legs. This may occur in normal feet subjected to unusually long hours of work, or excessive loads. Pronated or weak feet, because of faulty mechanics, are especially apt to develop symptoms of strain. Insufficient circulation due to varicose veins, arterial or cardiac disease, may be a contributing factor. An arthritic patient, especially one who has been confined to bed for some time, is apt to suffer greatly from this type of pain when he gets back upon his feet, even though the arthritic process has altogether spared the lower extremities.

Changes in the structure and flexibility of the foot due to arthritis render it very susceptible to ordinary functional foot disorders. The correction of these static disorders in stiff, painful arthritic feet is a difficult task requiring the utmost patience and ingenuity.

**Pain Due to Inflammation.**—Patients suffering from arthritis are subject to numerous aches, pains, and tender points throughout the entire body, sometimes associated with true exacerbations of the disease, sometimes dependent upon weather changes, and sometimes without any obvious cause. Because of the constant strain of standing, and the trauma of walking, these symptoms, when they occur in the feet, are much more disabling than elsewhere. The swelling may not be visible but tenderness is usually acute. It may be found in or about one or more joints. It may be found along ligaments or tendon sheaths. It is often beneath a weight-bearing point such as one of the metatarsal heads, or the tuberosity of the os calcis, or it may be found in any of the bony or soft tissues without any apparent reason. One of the sesamoid bones, or the base of the fifth metatarsal, or the posterior tip of the os calcis may be the site of an epiphysitis during growing years. In adult life, arthritic pain seems to have an especial predilection for these points.

Certain types of arthritis seem to affect certain foot structures, but too much dependence cannot be placed upon this fact. Gout has an especial affinity for the first metatarsophalangeal joint. Gonorrhea produces painful bursae or spurs beneath the os calcis and may even make that bone sore and tender along both sides. Ordinary nonspecific chronic arthritis often produces a moderate or extreme stiffness of the tarsal and midtarsal joints with a marked tendency to clawing of the toes and prominence of the metatarsal heads. This claw toe tendency is probably due to the atrophy of the intrinsic muscles of the foot and may progress to partial or complete dorsal dislocation of one or more of the toes, with numerous painful corns and calluses.

**Pain Due to Inflammation and Strain.**—Periarticular or intra-articular inflammation in any joint results in pain, swelling, and limitation of motion. In most of the numerous joints of the foot the range of motion is normally small and its loss is of no great importance, but a painful lesion in or about any one of these joints will cause remarkable changes in the attitude and function of the foot as the patient subconsciously attempts to protect the affected area. Such a position, assumed during the acute stage, may become the habitual one if the arthritic process leaves any residual stiffness, a sequela which is all too common. As might be expected, those joints subjected to constant use are most apt to be affected. The joints along the medial side of the foot, constituting the longitudinal arch, are those subject to the greatest strain. The first metatarsophalangeal is perhaps the most overworked joint in the entire body and the frequency of hallux valgus, hallux rigidus, and ordinary exostoses show how often it is the site of arthritic changes. It would seem that the position assumed to protect those joints, which together form the longitudinal arch of the foot, would be a position of varus, throwing the weight on the outer or strong side of the foot. In fact if the foot is supported in this varus position with adhesive strapping, or plaster, considerable relief is often obtained and deformity prevented. However, because the strain placed upon the midpart of the foot is greatly increased during progression when it is used as a lever to raise the heel and thrust the body forward, this lever action is unconsciously avoided. The tendency is to evert and



abduct the foot using it only as a pedestal, in a flatfooted stumping manner with most of the weight borne on the heel. The great toe assumes a position of valgus to avoid the strain of a "push off" or the painful motion of dorsiflexion. This position of external rotation and pronation, originally adopted to relieve the affected tarsal and midtarsal joints during walking, soon becomes fixed. Consequently, even when standing, the center of gravity falls well to the inner side of the weight-bearing area producing strain along the medial side of the foot in the calcaneoscaphoid or "spring" ligament, along the inner side of the ankle, and even on the inner side of the knee. The thighs roll inward and the extreme flatfooted posture results.

**Examination.**—The examination must be systematic and complete. The history should note any foot symptoms present before or after the onset of arthritis. Weak or pronated feet are more apt to be the site of arthritic changes than normal ones. Arthritic foot pain can usually be differentiated from that due to ordinary foot strain. The latter type is directly related to the amount of standing and walking done by the patient, and is not usually troublesome at night or upon arising in the morning. Arthritic pain may come on at any time and is often affected by weather changes. Also there may be considerable stiffness which can be worked out by moderate activity.

The patient should be examined standing and walking, noting posture and gait, especially the alignment of the legs in respect to the weight-bearing areas of the feet. All deformities should be carefully noted and the range of motion measured in the ankle, subastragalar, midtarsal, and toe joints. Rarely are all the joints of the foot involved at one time and treatment should be directed toward those especially affected. The amount of pain associated with each motion is of more importance than the actual range. The entire foot and leg should be palpated for tender points and painful areas, and the presence of calluses, corns, plantar warts, or fixed toe deformities noted. Painful hallux rigidus, dorsal dislocation of the second toe, and localized tender areas in the sole of the foot can be easily overlooked. The circulation of the extremity may be judged by the color, temperature, and pulsation of the dorsalis pedis and posterior tibial arteries. The presence of

varicose veins or ulcers should be noted. Anteroposterior and lateral roentgenograms are usually indicated.

**Differential Diagnosis.**—Every effort should be made to evaluate all the symptoms and analyze the foot pain to determine whether it is due to pressure, strain, or inflammation, and whether alterations in the general or local circulation are contributory factors. The success of any treatment depends entirely upon the correctness of this analysis. Specific diseases which produce foot symptoms must be considered. Syphilis, diabetes, and arteriosclerosis frequently cause foot



Fig. 133.—Neglected arthritic feet. Equinovarus right. Equinocavovalgus left  
Fixed deformities of toes Glossy tender skin

pain. Bone tumors, tuberculosis, spurs of the os calcis, march foot, Freiberg's disease of the second metatarsal head, dislocations of the toes, and gout, can usually be demonstrated in roentgenograms or ruled out by appropriate laboratory examinations.

**Treatment.**—In the treatment of the arthritic foot the main objects are to relieve pain, prevent deformity, and if possible preserve motion. Simple methods of protection, support, and active exercise are of much greater value than all of the diverse medical and physical treatments which enjoy periodic popularity. If the probability of residual stiffness is

kept in mind, disabling deformities can be prevented. Ankylosis, if it occurs, need not be in a position which makes the foot useless as a weight-bearing organ (Figs. 133, 134).

In the acute and subacute stages rest is essential. Weight-bearing should be entirely forbidden and the foot should be supported in a neutral position. A firm pillow between the end of the bed and the soles of the feet, and a cradle over them to eliminate pressure of the bed clothes, may be sufficient to relieve pain and prevent foot drop. Carefully fitted and bivalved plasters can be prepared, but these should be removed daily to avoid undue stiffness. A simple posterior wire splint is a very satisfactory foot support to prevent equinus (Fig.

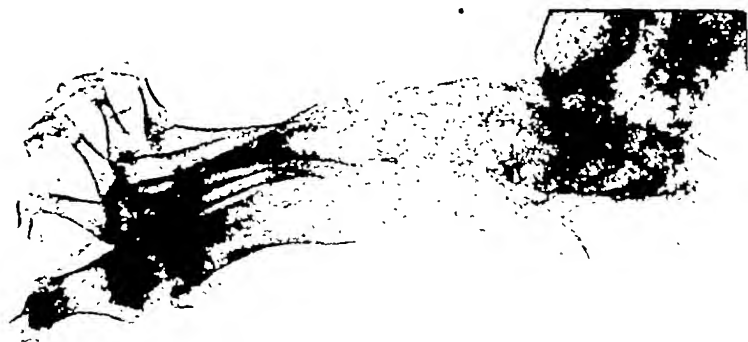


Fig. 134.—Claw toes and ankylosis with deformity caused by infectious arthritis.

135, 1). If there is a tendency toward claw toe deformity one can fit a special sandal with holes through the sole so that each affected toe may be strapped down against it (Fig. 135, 2). Compresses, local heat, baking, or diathermy often give considerable symptomatic relief. The prevention of foot deformities is much simpler than their correction and is of vital importance if the patient is ever to walk again.

As recovery progresses, nonweight-bearing exercises should be instituted before the patient attempts to stand. These are planned to restore mobility as much as possible and redevelop muscles which have usually undergone considerable atrophy. These exercises should systematically move all the joints of the foot and force all the muscles to function. Inversion and toe

flexion exercises are particularly important as eversion and claw toes are the deformities most apt to develop.

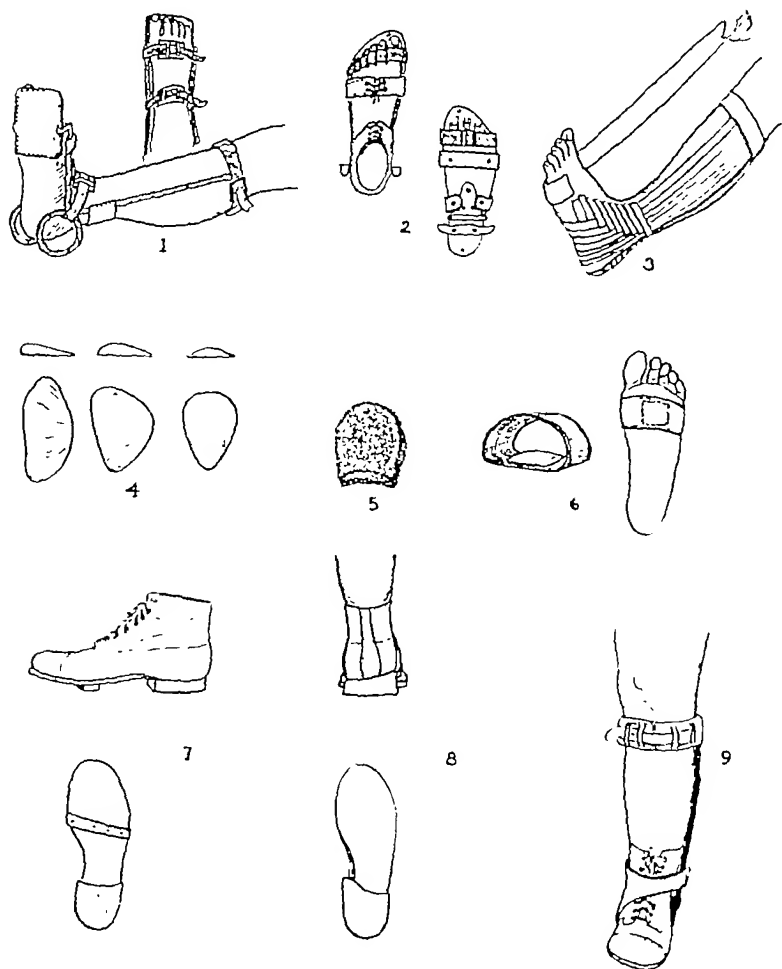


Fig. 135.—Methods of preventing deformity and relieving strain 1, Os-good posterior splint; 2, claw toe sandal; 3, inversion strapping; 4, pads for metatarsal or scaphoid regions; 5, sponge rubber for painful heels; 6, elastic metatarsal support, 7, metatarsal bar; 8, Thomas heel, 9, outside iron and T strap.

When the patient is allowed to stand, adhesive strapping for support and correction of pronation is usually very helpful

(Fig. 135, 3). Appropriate felt pads beneath the scaphoid bones or behind the metatarsal heads may be used to distribute the weight more evenly upon the sole of the foot (Fig. 135, 4). Elastic metatarsal straps with a metatarsal pad give welcome support and prevent spreading of the forefoot (Fig. 135, 6). Sponge rubber or dug-out heels are useful if the tuberosity of the os calcis is sensitive (Fig. 135, 5). A corn plaster or cut-out felt pad should be used to protect any painful bony prominence. If the metatarsal heads are tender, or the toes stiff and painful, a large metatarsal bar often gives great relief (Fig. 135, 7). Foot plates of various types can be fitted, but great care must be used in their design and they should be adjusted frequently. Molded leather supports are usually tolerated better than those made of metal. For a weak arthritic foot with pain in the scaphoid region or along the inner side of the leg, a well-wedged Thomas heel with an outside iron and an inside T strap is probably the best type of support (Fig. 135, 8, 9).

It must be understood that all of these conservative measures relieve sensitive and weak feet from pressure and strain, but cannot be expected to correct deformity. As the patient improves, exercises should be increasingly stressed, and when all signs of acute inflammation have subsided, motion can be encouraged by daily passive stretching of all the joints of the foot.

**Operative Treatment.**—Operative treatment should rarely be necessary unless conservative methods have been neglected. No operation should be attempted until the arthritic process is inactive. The safest and often the best way of correcting an arthritic deformity is by gentle stretching and application of plaster, repeated at short intervals. Stiffness is not overcome by this method, but, in the foot, a good weight-bearing position is more important than free motion. There is also the advantage that this stretching may be done even during the acute stage of the disease.

If gradual correction is not feasible or has failed, manipulation under an anesthetic may be indicated. To be effective, this must be followed by prolonged and careful supportive treatment and should never be attempted until some time after all acute symptoms have subsided. Although serious de-

formities may be corrected in this way, normal mobility is not usually regained.

Subcutaneous tenotomies of the extensor and flexor tendons of the toes and capsulotomies of the metatarsophalangeal joints will sometimes aid in the correction of deformed toes. Severe

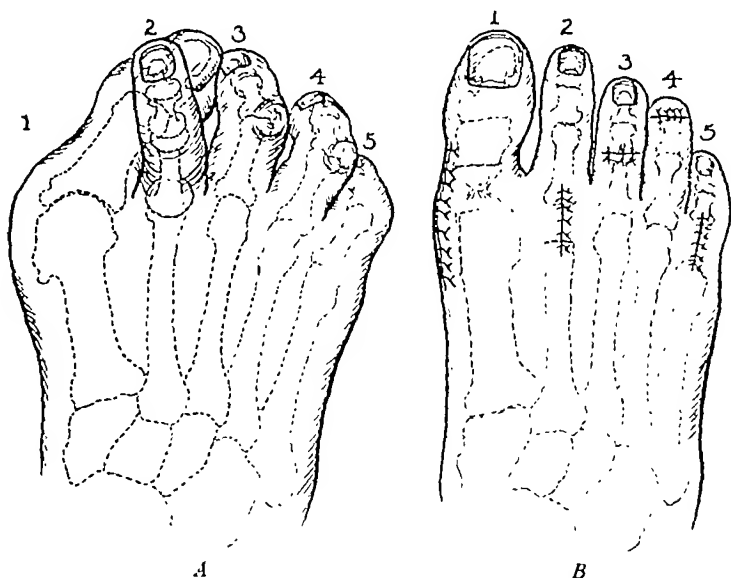


Fig. 136.—The operative correction of arthritic feet

*A-1.* Hallus valgus and hallux rigidus (bunion)

*B-1.* Hemiphalangectomy and exostosectomy

*A-2.* Dorsal dislocation of second toe.

*B-2.* Excision of head of second metatarsal

*A-3.* Hammer toe with painful corn.

*B-3.* Excision of corn. Fusion of interphalangeal joint (spiking operation)

*A-4.* Painful hammer toe with pressure on toenail.

*B-4.* Terminal Syme amputation removing toenail and distal phalanx

*A-5.* Claw toe projecting dorsally.

*B-5.* Excision of proximal phalanx

claw toe, especially if there is dorsal dislocation at the metatarsophalangeal joint, can often be completely and easily corrected by excising the entire proximal phalanx which usually projects upward. This "filleting" operation permits the remaining bones to drop plantarward and the toe to assume a

normal position (Fig. 136, 5). The period of convalescence is very short and no immobilization is necessary.

Hammer toe may be corrected by excision of the corn and arthrodesis of the deformed joint (Fig. 136, 3). However, it is often advisable to remove enough bone to allow free motion, as arthrodesis in good position requires very prolonged and careful splinting and adds one more stiff joint to an already too rigid foot. In most operations upon the forefoot one should remove bone freely and soft tissue sparingly or not at all.

Any metatarsal head which becomes too prominent and bears an undue portion of the body weight should be cleanly excised through a dorsal incision, allowing the weight to be distributed equally to the other metatarsal heads (Fig. 136, 2).

Corns and calluses require continued protection against pressure, or an operation correcting the bony abnormality which causes the pressure (Fig. 136, 3).

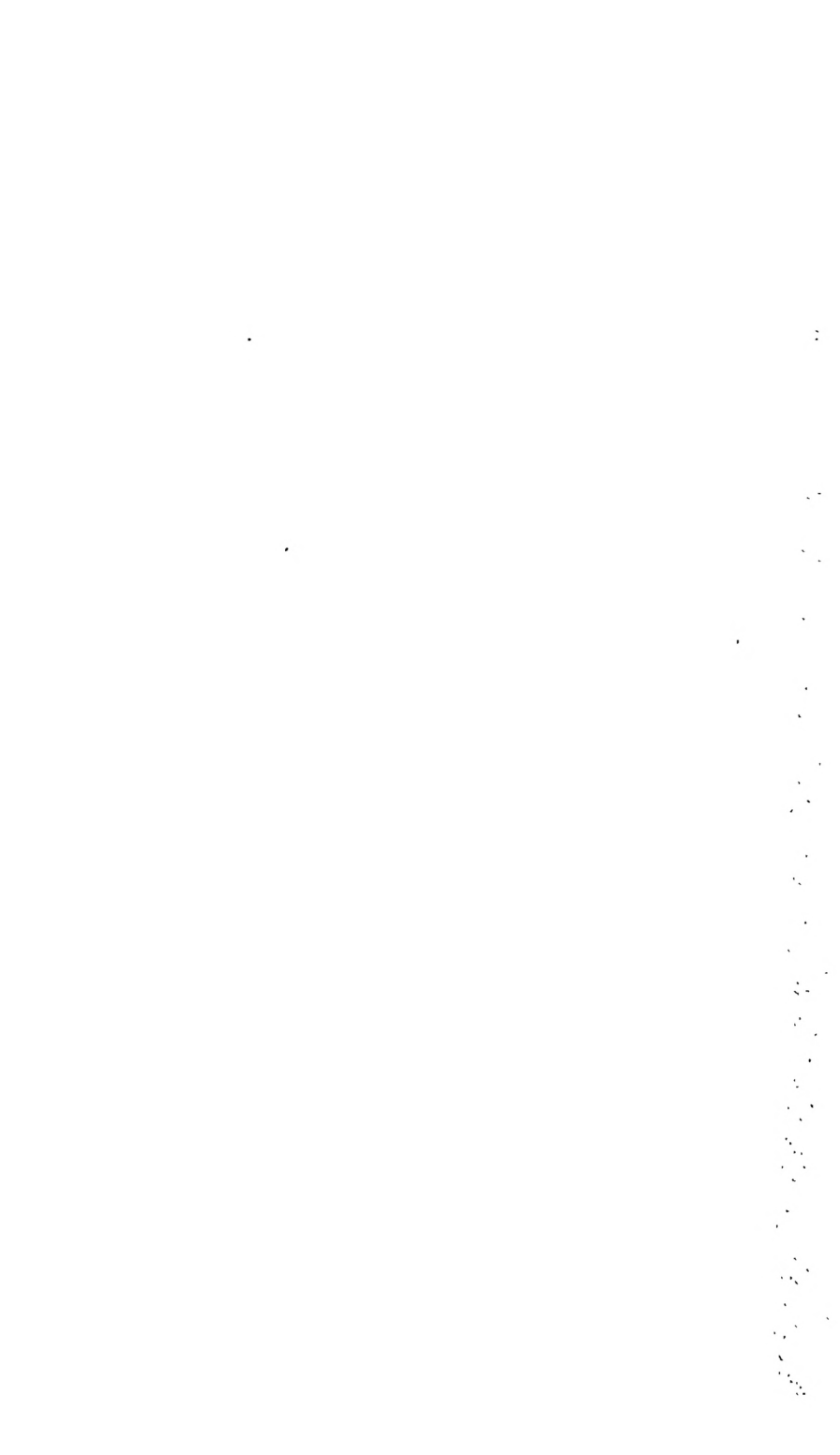
A painful deformity of the distal phalanx of a toe with pressure upon the nail may be easily corrected by a terminal Syme amputation removing the nail and distal phalanx (Fig. 136, 4).

Hallux valgus and hallux rigidus are very common in arthritic feet. Removal of the exostoses from the metatarsal head and excision of the proximal one half of the proximal phalanx usually corrects the deformity. The sesamoid bones and the weight-bearing area of the first metatarsal head should be avoided if possible, and an hour-glass constriction formed between the metatarsal head and the remainder of the phalanx to insure free mobility (Fig. 136, 1).

Amputation of one or even all the toes may be indicated if deformities are severe and the feet very painful.

Equinus, cavus, varus, and valgus deformities may require subastragalar, midtarsal, or even ankle arthrodesis with the removal of appropriate bone wedges. The foot should be re-aligned beneath the leg with a large smooth weight-bearing surface in contact with the ground. Painful motion should be eliminated from weight-bearing joints by arthrodesis, and from nonweight-bearing joints by wide excision.

Although there are numerous problems in the treatment of arthritis which defy solution, the prevention or correction of the painful foot deformities can be accomplished.





## CLINIC OF DR. CORNELIUS H. TRAEGER

### HOSPITAL FOR THE RUPTURED AND CRIPPLED

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#### FIBROSITIS

IN the arthritis clinic of the Hospital for the Ruptured and Crippled, New York City, we have had 900 admissions in the past two years. In a careful chart analysis of these cases we find a total of 262 patients who have as their presenting symptom pain in or about the joints with no external evidences of joint pathology such as swelling, redness, fluid, muscular atrophy or deformity. On roentgenologic examination of the joints involved we find no evidence of bony pathology. Yet these patients are truly ill. They have severe pain, frequently severe enough to prevent them from working or obtaining proper sleep; they have stiffness and disability. Of this group of 262 patients, 128 gave a history of having their complaint less than two years. One hundred and thirty-four dated the onset of their illness from two to eighteen years prior to admission. It is to be remembered that these patients were admitted to an arthritis clinic and yet they presented complaints which could not be segregated into the broad grouping of rheumatoid, osteo- or mixed arthritis. It is a fair assumption that if we were dealing with arthritis in these 134 cases of over two years' duration, some bony change would be apparent either grossly or roentgenologically. These patients showed no great variations from the normal blood chemistry values, blood counts or sedimentation rate. The paucity of abnormal laboratory or physical signs established these patients in a segregated group and for want of a better term we shall consider them as cases of fibrositis. Of all the entities grouped under the general heading of rheumatoid disease, fibrositis presents the most perplexity. There are some physicians who deny that fibrositis is

a clinical entity; others claim it the most important and the most widespread of all the rheumatoid diseases.

Much confusion attends the etiology, pathogenesis and classification of fibrositis. In a discussion on fibrositis last year Dr. Philip Hench made the following remarks: "If gout in America is a forgotten disease, fibrositis is an unknown disease, at least it is not known by that name. The disease is very widespread both in England and America, but very little is written about it in this country and the term fibrositis is practically unrecognized here."

Fibrositis, as the term indicates, is an inflammatory reaction of the fibrous tissue of the body. The term is well chosen and is based on the pathology of the disease. Frequently fibrositis is incorrectly used interchangeably with myositis but true myositis is uncommon. We are of course not including such diseases as myositis ossificans, tropical myositis, gonorrheal or syphilitic myositis or progressive myositis fibrosa or acute suppurative myositis. What the general practitioner terms as myositis or muscular rheumatism is in reality an involvement of the interstitial muscle tissue rather than the muscle parenchyma.

Fibrositis is a disease which is just as important as any other of the rheumatoid group. Patients with this ailment suffer just as acutely, are just as disabled, present the same financial problem as do those suffering with any of the other arthritides. It is important that our concept of fibrositis be clarified since so many of these patients are labeled as arthritics, with all the dread which such a diagnosis produces in their minds. So frequently doctors are prone to label these patients neurotics or psychotics because they cannot find any external evidence of pathology in the joints and no laboratory tests to support any other diagnosis.

This disease was originally described by Jaccoud as "rhumatisme chronique fibreux." Its present usage dates from the introduction of the term by Gowers in 1904 and by Stockman in 1933 and 1934. Fibrositis may be roughly classified into 3 groups: (1) primary fibrositis, the type which is the subject of discussion in this paper, which is an affection of fibrous tissue independent of pathology elsewhere in the body; (2) symptomatic or secondary fibrositis in which the changes in the interstitial tissues are secondary to some more deep-seated

lesions such as rheumatoid arthritis, spondylitis, rheumatic fever, gonorrheal arthritis, trauma, etc., and (3) senile fibrositis, representing the gradual fibrotic changes which take place in the later decades of life.

Fibrous tissue exists everywhere in the body and since it is subject to inflammatory reactions wherever situated, the anatomic distribution of the disease is of course widespread and it may be classified according to location.

First—panniculitis, that is, a fibrositis of the subcutaneous tissue which includes the areolar and adipose tissue. It is characterized by a loss of elasticity of the skin, which seems to be more adherent to the underlying tissue. Patients complain of a sense of chilliness and a diminution of sense of touch. Panniculitis is frequently painful. It is usually localized in the thighs or the back of the neck and occasionally it has a more widespread distribution. The most severe types of headache accompany cervical fibrositis. Telling considered it the most frequently found type of chronic or intermittent headache, the four diagnostic features of which are persistency, thickening, nape of the neck location and tenderness. The most intense headache I ever encountered was due to cervical fibrositis. This patient had been treated for sinusitis, had had several pairs of glasses made and had a complete neurologic survey, all without avail. She had resorted to narcotics in a desperate attempt to obtain some surcease from her suffering. The pain was limited to the occipital region associated with definite tenderness. Simple physiotherapy relieved her of all symptoms. When fibrositis involves the chest muscles it gives rise to the condition known as "pleurodynia" or intercostal fibrositis, which can be extremely painful and persistent and when confined to the left side of the chest is not uncommonly diagnosed as angina pectoris, or when bilateral is frequently mistaken for pleurisy. The chest is frequently tender and respiratory excursions limited. Breath and voice sounds are normal, friction rubs and râles are absent. Pain is increased with coughing, breathing or sneezing. Abdominal fibrositis is characterized by pain and tenderness elicited by "fingertip pressure," tender spots are frequently localized but may be multiple and occupy positions which are not usually affected by underlying visceral disease. Muscle spasm or rigidity, which is characteristic of

abdominal disease, is usually absent in fibrositis and the pain, which is constant in abdominal disease, is intermittent in fibrositis.

Second—intramuscular fibrositis (myositis or muscular rheumatism). In this group we must also include the inflammatory reactions in the fascial planes as well as the interstitial tissue of the muscle. It must be kept in mind that the parenchyma of the muscle is not involved but only the interstitial tissue. Intramuscular fibrositis may be localized or diffuse. This condition is frequently termed myalgia, neuromuscular pain, muscular rheumatism or myofascitis, and is characterized by pain on extremes of motion or intermittent subjective pain and muscle stiffness (jelling phenomenon). The pain may be persistent as in lumbago, may come on only with exercise or following strenuous work or may be intermittent. The pain here is localized, not at the joints but between them. Limitation of movement, if any exists, is produced solely by muscular stiffness rather than by pain or joint pathology.

Third—periarticular fibrositis which involves the joint capsule. This type of fibrositis is characterized by stiffness and soreness of the joints particularly after long periods of rest or on arising in the morning. Pain may also be elicited by abnormal stretching of the capsule. Tenderness is usually absent or fleeting in character. These symptoms are frequently transient in nature but occasionally persist.

Fourth—bursal fibrositis or bursitis. Bursal fibrositis is quite common and is to be distinguished from bursitis which is accompanied by increase of fluid in the bursal sac. In bursal fibrositis there is not the definite limitation of motion characteristic of true bursitis. Pain is only present on extremes of motion and tenderness is frequently absent. Calcification of the bursa is absent.

Fifth—tendinous fibrositis, or tendinitis, is a condition which involves the fibrous tissue of the tendons, is uncommon and more frequently found as Dupuytren's contracture.

Sixth—perineural fibrositis or interstitial neuritis is frequently called neuritis which is a misnomer. This generally affects the large nerves such as the brachial plexus and sciatic nerve. Sciatic fibrositis should be distinguished from a true sciatic neuritis. The fibrositic forms may be distinguished

from sciatica because in the former the pain is referred to the hamstring muscles and not the nerve trunk. In perineural fibrositis the pain follows the nerve distribution. There is no anesthesia or paresthesia over the area of distribution of the nerves. The pain of sciatic fibrositis is less severe and is confined to the muscles and is characterized by local soreness, tenseness and muscular stiffness. In brachial fibrositis there is tenderness over the brachial plexus above and below the clavicle and pain is elicited only with abduction of the arm.

**Etiology.**—The etiology is of course unknown. In the analysis of our 262 patients we find that the disease has frequently followed chill, fatigue, trauma or chronic strain, infection, nervous exhaustion and very frequently follows influenza or respiratory infection. Focal infections were frequently found in many of these patients. Some authors stress the importance of chilling or climatic change. Others emphasize the importance of focal infection, metabolic disorders, intestinal toxemia and allergy. There is as much confusion with respect to the etiology of fibrositis as there is in chronic arthritis. It is quite possible that any or all of these factors may act as etiologic or precipitating factors in the production of this disease.

**Pathology.**—Here again we are beset with many difficulties for the simple reason that patients object strenuously to biopsies. Slocumb describes the pathology as follows: "In stage one there is an inflammatory serofibrinous exudate of low grade with proliferating fibrositis and newly formed blood vessels. In stage two, if the inflammatory process is more severe and of longer duration, indurated, local, tender, thickened tissue or frank, gross, subcutaneous nodules may be produced. They may become firm and in them may be found dense inflammatory hyperplasia of fibrous tissue, thickened blood vessels and inflamed nerve fibrils. There is no leukocytic reaction. In stage three, when the inflammatory activity has passed spontaneously, or as the result of treatment, some indurations may disappear. Others remain as painless thickenings or nodules. Fibrous, tendinous contractures, capsular thickenings may affect such joints as the shoulders and palms."

Most writers stress the importance of the fibrositic nodule. In our group of patients these fibrositic nodules were con-

spicuous by their relative infrequency. When present they were usually very deep-seated and would have presented difficulties for their surgical removal. A more frequent finding was a generalized solidness or spasticity of the muscles involved. The fibrositic nodules vary in size from a "pea" to an "almond," and are not to be confused with the subcutaneous nodules found in rheumatoid arthritis. Cyriax believed that these nodules were produced by small localized muscular contrac-

### DIFFERENTIAL DIAGNOSIS

#### *Fibrositis*

Limited to a definite area.  
Tenderness is a variable factor.

Stiffness present or "jelling phenomenon" which disappears very quickly after exercise or movement. Very frequently the first symptom which the patient with fibrositis complains of is this "jelling" or stiffness of the joints after long periods of rest, such as sitting in a theater seat, playing bridge or on arising in the morning.

Muscular atrophy rare.  
Synovial exudate never found.  
Pain elicited only on extremes of motion, or any type of forced movement which produces tension of the capsule.

Pain frequently relieved after moderate exercise.

Frequent remissions.

Systemic manifestations are uncommon.

Capsular thickening may be present.  
High sedimentation rate and secondary anemia rare.

No roentgenologic evidence of bony involvement.

#### *Rheumatoid Arthritis*

The rule is polyarticular involvement.  
Tenderness frequently outstanding symptom.

Stiffness persists after motion or exercise.

Muscular atrophy quite common.  
Synovial exudate a frequent finding.  
Pain on motion of affected joint characteristic symptom.

Painful following exercise.

Remissions uncommon.

Systemic disease frequently attended by slight rise of temperature, loss of weight and appetite, secondary anemia and low blood pressure

Capsular thickening may be present  
High sedimentation rate and secondary anemia frequent occurrence  
Roentgenologic evidence of bony pathology is the rule

tions and that when nodules rapidly disappear under various measures, it is the muscular contraction that disappears, leav-

ing a residual nodule too small to palpate. The importance of these fibrositic nodules is still undetermined and until more of these nodules and their adjacent tissue in various stages of the progression of the disease are examined, our judgment should be reserved.

**Prognosis.**—The prognosis of fibrositis is good. It is the most tractable of all the rheumatic affections. Where the onset is acute, rapid cure is the rule. In the more chronic cases careful treatment must of necessity be persisted in for longer periods of time. The prognosis of course depends on the etiologic factors encountered and on the general condition of the patient. Favorable results can only be obtained by the careful elimination of etiologic factors and persistence in using all the available methods of treatment.

**Treatment.**—The treatment of course divides itself into two main groups, general and local. Rest is important in the relief of pain but should be confined only to the acute stage of the disease. Exercise should be gradually instituted. Patients suffering from fibrositis are affected by change of weather and it sometimes becomes important to change the climatic surroundings of such patients. Cold and dampness militate against recovery and a change to warmer, more pleasant surroundings is frequently advisable. Many of the cases of "arthritis" who are cured by trips to Florida or Arizona were probably not arthritis at all but really fibrositis. The complete change of environment is sometimes helpful in relieving the patient of the stress and strain of his everyday existence. Drugs are only of importance in the relief of pain and salicylates are most frequently employed and should be administered in adequate doses.

Many writers stress the importance of vaccines in the treatment of fibrositis. Scott extols the virtues of a lipovaccine injected into the fibrositic area. May states that the best results are obtained by a combination of vaccine treatment with physical therapy. Vaccines in this connection are not used for their specific effect but more for their nonspecific protein effect. A stock vaccine of the mixed streptococcus type is the one most frequently employed.

The question of the importance of diet is still in dispute. Some writers think it of great importance, others think it plays

no rôle in the treatment of this disease. A well-balanced diet which provides for proper vitamin intake and regulated with respect to the patient's body habitus is to be recommended.

*Gastro-intestinal Treatment.*—Albee stresses the importance of intestinal toxemia as an etiologic factor in fibrositis and strongly recommends the use of colonic irrigations. May states that he is convinced that the most common cause of toxemia producing fibrositis comes from the gastro-intestinal tract. Where intestinal stasis or intestinal toxemia is present colonic irrigations have proved to be useful adjunctive therapy.

Foci of infection when present should be removed if the patient's condition warrants it. Spectacular results have been observed following the removal of obviously infected teeth or tonsils or by proper treatment of involved sinuses. Hunt reports 2 cases of fibrositis with *Bacillus coli* infection in the genito-urinary tract who recovered only when the urine became sterile. Focal infections in the appendix, gallbladder, cervix, tubes or prostate are considered to be less commonly involved although their importance is stressed by various writers.

*General Physical Therapy.*—Where fibrositis is more or less generalized, cabinet baths prove useful. Hot Epsom salt baths are frequently recommended. General massage is important only in the stimulation of the general vasomotor system and the lymphatic circulation of the body.

*Local Measures.*—There are many forms of local therapy and all of them are important. To rely on any one particular method of treatment invites failure. The object of course is to relieve pain and to stimulate the absorption of the infiltration. The most frequently used method is diathermy; ultra-short-wave and the conventional diathermy are the generally accepted methods. These frequently increase the subjective pain temporarily but will usually bring about improvement. Histamine ionization, which is the use of galvanic current for the introduction of drugs into the tissues, is said to be of more value in the acute stages of this disease than in the chronic stages. MacKenna claims it can completely cure the condition. Infra-red radiation, especially to the smaller joints, is an excellent mode of therapy. Hydrotherapy is another excellent adjunct to treatment and may be utilized in various



forms, either total immersion in specially prepared tanks, or pools filled with warm water or whirlpool baths or just hot soaks, have proved efficacious. Contrast baths or Scotch douches have also proved useful. Paraffin baths for the extremities frequently produce excellent results. In the procedure the arm or leg is immersed in molten paraffin at temperatures between 110° and 120° F. several times until a glovelike coating is produced. The extremity is then wrapped in a towel for twenty minutes, following which the paraffin is peeled off and gentle massage instituted. Use of the static current has fallen into disfavor and is seldom used in the treatment of fibrositis.

The most important of the local measures is of course massage. This should be done gently at first, followed by more vigorous massage as treatment progresses. It is important that the movement of the joints be maintained by passive motion from the onset. Vigorous massage will eliminate the muscle stiffness and frequently cause the disappearance of the fibrositic nodules. Such treatment will of course be painful and if the patient finds it difficult to relax his muscles sufficiently because of the pain, analgesics should be employed prior to the treatment and the preliminary baking should be prolonged. Massage, of course, should always be preceded by heat applied in some form. Massage never should be used in the acute phase. Heat should be applied without massage during the stage of effusion.

**Conclusions.**—Fibrositis is a definite clinical entity, little understood or appreciated in this country. It is of frequent occurrence and is important from the standpoint of pain, disability and financial loss to the patient.

Etiologic factors are usually chill, trauma, fatigue and infection.

Pathology is represented by inflammatory infiltration of the interstitial tissues of the body.

The various types of clinical manifestations of fibrositis are described in detail.

The differential diagnosis is described in detail.

The disease is characterized by paucity of abnormal laboratory or roentgenologic data.

Treatment is divided into general and local therapy, a detailed description of which is found in the text.

The prognosis is good.

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## CLINIC OF DR. MARTIN HENRY DAWSON

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### A NOTE ON THE OCCURRENCE OF PSORIASIS IN RHEUMATOID ARTHRITIS\*

THE association of psoriasis with chronic arthritis has long been a matter of clinical observation, especially among members of the French school of medicine. According to Garrod and Evans, Alibert, in 1822, was the first to recognize the occurrence of joint pains in psoriasis and since his time many observers have commented on the occurrence of these apparently diverse disease processes in the same patient. One variety of this symptom-complex has occasioned particular interest and has been designated by various terms such as *psoriasis arthropathica*, *arthropathia psoriatica*, *psoriasis arthritica* or *psoriatic arthritis*. By these terms there is generally understood a more or less severe form of chronic arthritis of the rheumatoid type associated with extensive psoriatic lesions. Many authors insist that these terms be restricted to cases exhibiting the following features:

1. The psoriatic lesions are atypical in character and distribution. The eruption is exudative in nature, associated with waxy, translucent papules and large abundant scales. The hands and feet are frequently affected and there is a marked tendency for the process to involve the nails.
2. The onset of the psoriasis may precede, or coincide with, the onset of the arthritis but exacerbations of the one are usually accompanied by exacerbations and remissions of the other.

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3. The arthritis is characteristically rheumatoid in type with the curious exception that the *terminal* interphalangeal joints of the hands and feet are frequently affected.

Other observers believe that the term *psoriasis arthropathica* should not be so narrowly restricted and that it should include all cases of psoriasis and rheumatoid arthritis. There is general agreement that the association of psoriasis with osteo- (degenerative) arthritis is a pure chance phenomenon.

We have had the opportunity of studying 19 cases of rheumatoid arthritis in whom psoriatic lesions were present. Seven of these cases conformed to the requirements of *psoriasis arthropathica* in the narrower definition of the term. In 7 others the psoriasis showed the atypical, exudative type of lesion but the arthritis was of the classical, rheumatoid variety. In the remaining 5 cases neither the psoriasis nor the arthritis showed any unusual features.

Our observations lead us to question the advisability of restricting the term *psoriasis arthropathica*, or its synonyms, to those cases which show atypical manifestations of both diseases. It appears that a certain number of cases of rheumatoid arthritis develop psoriasis (actually less than 2 per cent) and that a certain number of psoriatics develop rheumatoid arthritis. The occurrence of these two disease processes in one and the same patient is an interesting phenomenon and merits further study.

## CONTRIBUTION BY DR. K. G. HANSSON

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### MASSAGE AND EXERCISES IN ARTHRITIS

MANY attempts have been made to find a specific remedy for arthritis. All of them have failed, as could be expected, because arthritis is not due to one etiology. However, in the control of arthritis we have certain principles that have been tried out for centuries, and are still used, while other remedies come and go. Wherever arthritis is treated, massage and exercises have always occupied an important part in management of the arthritic patient. It is being used empirically by many, although we know fairly accurately the indications and the contraindications. Sir Robert Jones has said that the value of massage is too well established to require defense. Yet it cannot be denied that many of the ideas prevalent as to its methods of use are often vague, and doctors who have made a close enough study of the subject to give definite directions to a technician are still fewer than they should be. The main physiologic actions of massage should be known to the doctor, although the actual practice of it must be left to properly trained technicians. The physiology of massage may be briefly reviewed under *mechanical action* and *reflex action*; only the former concerns us here. We may consider the mechanical action under three headings:

1. Assistance to circulation of blood and lymph. The unit of our body is the cell and the cell metabolism determines our body metabolism. The absorption into the cell of carbohydrates, fat and proteins and oxygen, and the discharge of residues of the cell metabolism can be activated by massage; this can fill and empty the capillaries. The capillaries are often contracted and tortuous in arthritis. The stroking along the veins will help empty these and accelerate the blood flow

through the capillaries. The same massage will help the return of lymph and prevent or relieve stasis. The mechanical action of massage on circulation is a pressure-suction action which helps the vasomotor system, and restores the proper balance in the cells.

2. Massage helps to break up and absorb adhesions. If India ink is injected into the knee joints of a rabbit, and only one joint is massaged, we will find that the India ink will be absorbed readily in the joint which is massaged, while it will remain in the other joint. The invasion of a joint by arthritis will show congestion, productive inflammation, and connective tissue proliferation both in the joint and around it, resulting in a stiff joint. Massage will help to restore such a joint to normal after the acute onset.

3. By alternating pressure and release we can restore the tone of muscular tissue, and the hollow viscera. This manipulation of skeletal muscle is well known, but the abdominal massage is not utilized as it should be. It is especially beneficial in bedridden patients.

The technic of massage can be reviewed under stroking or effleurage, kneading or petrissage, and hacking or tapotement.

*The effleurage* is a stroking movement of the palm of the hand sliding over the patient. We speak of superficial and deep stroking. The difference is in the force applied. The superficial stroking should be light, rhythmical, and unidirectional, following the venous flow; the actual stroke should be of the same length as the return stroke. *Effleurage* is used for the mechanical effect on the circulation.

*The kneading* is done by the palmar surfaces of the hands, the heel of the hand, the thenar eminence, all the fingers or the thumb alone. The soft tissue is kneaded by circular motions. This hand movement is used to restore the normal balance of the soft tissue, and to help absorption.

*Tapotement* is any hacking, beating, or clapping with the palmar surface of the hand, the ulnar surface of the fingers or hand, and by a loosely held fist. The main effect is stimulation to the muscular tissue, and the nervous tissue. The well-trained technician will know how to combine these hand movements in individual treatment, the same as an artist blends his colors.

We may set certain rules for the patient undergoing massage. He should always lie down, undressed, well supported and relaxed. Massage should not be given when the circulation is needed to take care of the digestion. Stimulative treatments should be given in the forenoon, recuperative or sedative treatments in the afternoon or evening. The skin of the patient should be clean and warm.

The rules for the technician include cleanliness and neatness in appearance. The hands should be warm and dry. Intelligence is more important than strength. Exercises are usually included in the treatment, so that the technician should be well trained in exercises as well as massage. I am in a position to meet more technicians than probably any one in the country, and it is a sad reflection on the credulity of the medical profession to read their letters of recommendation for masseurs who have the most inferior training, or no training at all.

Massage is often associated with various medications, which have been credited with beneficial action in arthritis. However, any absorption of medication through the skin is questionable. What is needed, therefore, is only a lubricant. These are of two main groups, the fatty acid and the powder. Most of our ointments are in the fatty acid group. These should be used on dry, hairless skin, and for local treatments. The powder, such as talcum, should be used on moist or hairy skin, and for general treatments. Both ointments and powders can be scented with volatile oils, but these are of olfactory benefit rather than therapeutic value.

In the typical patient with rheumatoid arthritis, we deal usually with an individual who is below par generally; has poor muscular tone and atrophy. The treatment should therefore be directed toward a general building up; the massage should be concentrated on the soft tissue, especially the muscles, and the joints should be avoided. This is paramount in the bedridden patient with acute arthritis. The massage should be light. We should avoid tiring the patient. In subacute and chronic cases the massage can be used on the joints. We are often confronted with unbalanced muscle groups as part of the picture of beginning contracture and deformity. In such unbalanced muscle groups, stimulating massage should be used

on the elongated muscles and relaxing massage on the shortened muscles.

In osteo-arthritis the patient is often overweight, and general massage is given to counteract the inactivity. The local massage can be given directly to the joint, and can be more vigorous than that given in rheumatoid arthritis.

Osteo-arthritis so commonly involving the fingers can be successfully treated with paraffin dips preceding massage. Ordinary laboratory paraffin is used, which melts at 150° F. Let it cool to 130° F., then have the patient dip his hands into the paraffin a dozen times, cover them with a towel for fifteen minutes, then massage each finger individually. This preparation for massage by paraffin can be used on any joint of the body, and when dipping is not feasible we apply it by means of a brush. Preliminary heat for the whole body, however, is best done by a heat tent, *i. e.*, a tent made of a sheet, containing a lamp, is arranged over the patient.

The prescription of massage in the management of the arthritic patient should be for a specific purpose. It should state whether general massage is desired as a tonic for the patient, or as a remedy for inactivity. If local massage is indicated for an atrophied muscle group or to promote absorption in a given joint, I believe that better results could be obtained if the doctors were more discriminating in their prescription of massage in the management of the arthritic patient.

#### EXERCISES IN ARTHRITIS

The symptoms that will bring most arthritic patients to seek medical advice are pain and stiffness. The pain is usually associated with motion in a damaged joint; this will result in stiffness, later deformity. The question of rest versus exercises in the treatment of arthritis has always been difficult to answer. It is evident that we must rest an acute arthritic joint, but when should the rest stop and movements be started? In a general way I believe that it is safe to say that the sensation of pain is given us for a protective purpose, and therefore anything producing pain should be contraindicated. However, this must be modified, or half the human race would go to bed and remain there. The painful sensation from the joint surface



itself can be used as a criterion for activity in a joint, but the stiffness from the muscles, ligaments, and capsule should be differentiated from true joint pain.

We may simplify the discussion of exercises if we consider them under these three headings:

1. Body mechanics reconstruction.
2. Local active exercises.
3. Passive manipulations.

**Body Mechanics Reconstruction.**—It is impossible to classify arthritis into definite groups, but we are all conscious of certain types which we recognize as the rheumatoid or osteoarthritic variation. These types are not inclusive, nor are they always pure. However, they do serve to direct our attention to arthritis as a disease not of the joints alone, but as a widespread disorder of the whole body machine.

Body mechanics is the function of all the parts that make up the human body. It deals with the skeleton, the muscular system, the nervous, gastro-intestinal, circulatory, respiratory, renal and endocrine systems. When we study the arthritic patient from the point of view of body mechanics, we may easily differentiate between the rheumatoid type and the osteoarthritic type.

*Rheumatoid arthritis* is usually found in the slender anatomic type of person between the ages of twenty and forty. The body as a whole sags. The head sags, the back, the chest, the shoulders, abdomen, knees and feet all sag. This outside appearance of failure corresponds to the actual failure of the body to do its work as shown by underweight, weakness and muscular atrophy, low vital capacity, and low basal metabolism. The inefficiency of the circulation shows itself in low blood pressure, secondary anemia and subnormal temperature. It is evident that the organs and viscera responsible for these functions are working under great disadvantage, and the body as a whole presents a decreased resistance to invading micro-organisms.

The correction of such faulty body mechanics presents a rather complex problem. We must align the skeleton in its proper interrelation. The head must be so balanced on the cervical spine that the respiration is unobstructed, the circulation to the head is free and there is no sagging of the cervical

fascia which helps to support the diaphragm and the abdominal viscera. This is done by carrying the chin in. The spine will show either an increase or decrease in the normal curves, and this should be readjusted by postural instruction in having the patient maintain the corrected alignment for longer and longer periods until it becomes no effort at all. The shoulders should be carried low and the thorax high. A very important point in the skeletal correction is the pivot point between the spine and pelvis. The lumbosacral angle is often increased, tilting the pelvis forward, thereby straining the ligaments in the lumbar region and permitting the viscera to spill over the brim of the pelvis pressing against the lower abdominal muscles. Here we should attempt to bring the sacrum under the fifth lumbar vertebrae in good weight-bearing position.

If a line is drawn from the mastoid process, the acromial process, through the greater trochanter and external malleolus in the standing position, this line should be straight. When a plumb line falls through the middle of the patella and the second toe, we have the proper weight bearing on the lower extremities. To maintain this proper weight bearing on the feet is most important in order to prevent damage to cartilages of feet and knees, hips and lower spine.

The skeleton is dependent on the muscular support. In normal conditions there is a perfect balance between the antagonistic muscle groups. The head is balanced by the neck muscles which act as guy ropes; the shoulder girdle is balanced in the horizontal plane by the pectoral and the trapezius muscles; the lumbosacral angle is maintained by the abdominal muscles and rectus femoris in front, and the gluteus maximus and hamstrings in back. We find the same muscle balance between the quadriceps and hamstrings responsible for the control of the knee. In the foot we must have balance between the flexors and the extensors, the invertors and evertors in order to maintain the proper weight bearing and locomotion. When this balance is disturbed we set up abnormal stress, strain and pressure on the corresponding joint cartilages and ligaments. This sets the stage for an arthritic invasion of the joints.

The heart and the diaphragm are of great importance in the analysis of body mechanics. The function of the diaphragm is not only a respiratory one, it also has a definite effect on the

thoracic and abdominal veins. The lengthening and shortening of the veins attached to the diaphragm is important in the pumping of the venous circulation. The position and the excursion of the diaphragm can be analyzed by x-ray or fluoroscopic examinations. By diaphragmatic exercises we can improve the excursion of the diaphragm and secondarily help the circulation.

A vital capacity study of patients with rheumatoid arthritis showed a persistent low percentage of normal. The average vital capacity in a group of 50 patients was about 25 per cent less than normal. This vital capacity was calculated from the height and weight, which gives the body surface. This body surface with spirometer readings gives you the vital capacity of the lungs. This low vital capacity is what you might expect in the dropped chest. This sagging of the thorax is important because it serves as muscle attachment of the respiratory muscles. These muscle attachments are brought closer together, thus making their function mechanically less efficient. This is especially true of the diaphragm. Respiratory exercises therefore are essential in the reconstruction of poor body mechanics as related to rheumatoid arthritis.

The abdominal viscera and the pelvic organs vary considerably in their position, but we must recognize certain limits to the displacement. A stomach above the umbilicus undoubtedly functions better than one in the pelvis. The sagging of the abdominal viscera is usually compensated, but the uncompensated visceroptosis is followed by malfunction and congestion. This will add to the poor health of this type which is so often a victim of rheumatoid arthritis. We must counteract the tendency to visceroptosis by increasing the tone of the abdominals with exercises. Abdominal exercises complete the picture of the reconstruction of poor body mechanics.

*Osteo-arthritis* is more common in the heavy-set individual with a tendency to overweight, high blood pressure, and good muscular development. He starts with good body mechanics and acquires visceroptosis and poor posture. It is more common in people over forty. The arthritic changes are found in the joints which are subjected to weight bearing and mechanical stress and strain. Faulty body mechanics in conjunction with poor metabolic chemistry is the cause of osteo-arthritis, rather

than infection. Exercises in the management of osteo-arthritis are based on a correction of faulty body mechanics and in addition general exercises for the maintenance of muscular tone and the reduction of weight. This type of patient should be kept active and especially encouraged in exercises without complete weight bearing such as swimming, horseback riding, etc.

From this very brief review of types of arthritis, we might suspect that body mechanics play a very important part in both the production and the treatment of chronic rheumatism.

**Local Active Exercises.**—Although arthritis is mainly an involvement of the articulations, the interrelation between the joints and the muscles responsible for the joint action is such that one cannot be disturbed without affecting the other. While our therapeutic efforts are focused on the joints themselves, we cannot afford to neglect the muscles. An inactive joint will produce inactive muscles which will lead to disuse atrophy. This atrophy affects the muscles in various degrees and in a general way we may say that the extensors and abductors will atrophy sooner than the corresponding flexors and adductors. This will lead to unbalance of muscles and result in contraction deformities.

As an example we may consider the knee joint. The leverage, muscle power and phylogenesis are all in favor of the flexors. It is a common experience that the quadriceps atrophies readily, and it is therefore important to start the patient early on quadriceps exercises. This contraction-relaxation of the quadriceps can be performed without moving the knee joint, and should be done at least two minutes every hour. This simple exercise will maintain the tone of the quadriceps, prevent atrophy and counteract flexion contraction. The same is true of the extensors of the ankle and toes, the extensors and abductors of the hip, and corresponding muscle groups in the upper extremities.

The characteristic deformities of the hand and fingers in chronic rheumatoid arthritis have always been accepted with resignation by patients as well as by the medical profession. The typical deformity in rheumatoid arthritis is due to disuse, which produces an unbalancing of the muscular pull. This results in flexion deformity in the metacarpophalangeal joints and terminal interphalangeal joints, and extension deformity

in the first interphalangeal joints. To prevent this we must supply adequate circulation by means of paraffin dips and some form of activity for the fingers. These exercises should take the form of gentle continuous movements such as you get in knitting, piano playing, and typewriting. I still have to see the typical finger deformity in an arthritic patient who has had to keep her fingers active during the major part of the day.

**Passive Manipulations.**—Passive stretchings of arthritic joints are used much less today than in former years. However, they have been used for so many years that they must have something to recommend them. It is probably a question of selecting the proper cases. We all recognize that a joint with arthritic pathology often shows periarticular fibrositis and muscular spasm. The ideal condition for manipulations is slight change in the joint and marked periarticular involvement. This is found in both rheumatoid arthritis and osteo-arthritis in subacute and chronic stages.

Two principles underlie these passive manipulations. The first one is that the joint surfaces should be separated, or maximum traction should be exerted on the joint. The second one is that the motions undertaken should be based on the normal kinesiology of the joint in question. The first point is illustrated in the manipulation of a shoulder. The patient is in a sitting position, and the manipulator places his knee in the axilla, thereby exerting traction in the shoulder joint. From this position the shoulder is carried through flexion, extension, abduction, adduction, external and internal rotation.

The second point is shown in the manipulation of the ankle and foot. The patient lies on his back with the leg under treatment abducted in such a way that the manipulator, standing inside the flexed knee, can exert countertraction against the thigh with his body, and actual traction on the foot with both hands. One hand grasps the heel, the other hand grasps the forefoot. While maintaining traction we go through normal motion in the tibio-astragalar joint, the astragalocalcaneal joint, the midtarsal joint, the tarsometatarsal joints, the intrametatarsal joints, the metatarsophalangeal and interphalangeal joints.

This type of manipulation under traction is easier on the joint than the old method of forced stretching on pressure

against the joint. If a hip joint is to be manipulated, have patient on back, grasp the extended leg by the ankle, lean backward and use your weight for traction, while you go through the hip motions. This applies to all joints of the body. Such manipulations may produce temporary pain, but should not cause a sleepless night, or discomfort the next day. Often the patient experiences a sensation of better control of the joint and less apprehension of defeat in the function of a joint.

We may summarize our ideas on massage and exercises in arthritis by saying that these two valuable agents are of great importance in the management of the arthritic patient. We may go further and say that they are indispensable in arthritic therapeutics. They are not specific remedies, but are complementary agents to every treatment that is being used in arthritis. Instead of leaving the prescription of massage and exercises to the gambling instinct of the technician, it would undoubtedly benefit the patient if the doctors were familiar with the physiologic action of these agents, and were able to prescribe them for his patient for a definite purpose.

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### ELECTROTHERAPY IN CHRONIC ARTHRITIS

It is the present consensus of opinion that chronic arthritis is a "constitutional" disease with local changes in the joints as well as disturbances in the circulation of the skin and in general metabolism. In some cases a primary focus of infection may be responsible for supplying the stimulus for the systemic and local changes. Physical agents offer a wide range of potent measures for influencing the general condition—the focus of infection, the changes in the joints and also for relieving local and general pain and safeguarding and restoring function.

The principal physical measures in the treatment of chronic arthritis are heat, massage and exercise; in addition, certain counterirritation measures. The various forms of these measures are considered in different sections of this symposium and this presentation is to be confined to the consideration of electrical and radiant energy. In actual practice one cannot separate these measures from the other forms of physical treatment. The simpler electrical measures are important from the standpoint of the general practitioner because they lend themselves to well-controlled use in the office and they are also valuable for properly supervised home treatment.

#### ELECTRICAL AND RADIANT ENERGY IN THE TREATMENT OF CHRONIC ARTHRITIS

- (A) General or systemic measures:
- Large radiant heating units.
  - Electric light cabinets.
  - General diathermy or short-wave diathermy.
  - Heliotherapy.
  - Galvanic baths.

## (B) Local measures:

- Luminous heat and infra-red radiation.
- Diathermy and short-wave diathermy.
- High frequency sparking (Oudin current).
- The galvanic current.
- Ionization with vasodilating drugs.
- The static wave current.
- Low tension wave currents.

**Electrical Heat.**—Thermal measures are potent agents in influencing circulation and metabolism. In rheumatic arthritis the heat-regulating apparatus is disturbed and the circulation is out of order, as manifested by its variations in the skin and extremities, especially the fingers and toes. Other parts of the body, especially the organs of the abdomen, which are not accessible to observation undoubtedly are the seat of the same variations. The vasomotor control is unstable. The basal metabolic rate is changed and the blood pressure is low. Systemic heating therapy in all forms of chronic arthritis results in the acceleration of the pulse rate, a general vasodilation in the skin; the circulating blood volume is increased, while the alveolar carbon dioxide tension and the alkalinity of the blood show a decrease. Metabolism always shows a considerable increase on any rise of body temperature; according to the temperature law of Van't Hoff, for every rise of  $10^{\circ}$  C. the rate of oxidation is increased two and one-half times.

The clinical object of systemic heating therapy is stimulation of the general circulation and the increase of body metabolism; the local changes are only indirectly affected, yet in many instances following general thermal treatment there is a decrease of pain and swelling and functional improvement in the affected parts. Rheumatic exudations have been likened to smoldering foci of disease, and heat—properly used—often effects their resorption.

For mild general heating in physicians' offices *large incandescent lamps* or *infra-red generators* of 1000 to 1500 watts capacity may be applied for one-half hour or longer. Mild body heating may also be obtained from high frequency sources in the form of general diathermy, short-wave diathermy and in occasional instances autocondensation. *Electric light cabinets* are employed in the institutional treatment of arthritis; the



duration of each treatment is from eight to fifteen minutes, according to the tolerance of the patient; it is usually followed by a tepid shower and a half-hour rest.

*Artificial fever treatment* has found a fairly extensive clinical use during the past few years. General diathermy, short-wave diathermy in a condenser and electromagnetic field and heating boxes have been utilized to produce hyperpyrexia. The consensus of opinion is that such treatments, although frequently very exhausting to arthritic patients, produce no other than temporary improvement in the general condition and the local symptoms. For this reason there seems to be little advantage of fever therapy in rheumatoid arthritis over the time-honored systematic use of mild general thermal measures. In acute and chronic arthritis due to gonorrheal infection, on the other hand, fever treatment has proved almost specific and is being now employed generally, if local treatment fails to clear up the affected joint.

The selection of a systematic thermal measure must be made on the basis of seasoned clinical experience and within the limits of the expected individual tolerance. No general heating measures should ever be instituted in a haphazard way and without definite indications. Provision must be made for patients to cool off and rest after any general heat treatment. A well-planned course of general thermal measures should be followed by a period of no treatment or be alternated with suitable local treatment.

*Local heat* treatment has as its object the increase of local blood and lymph circulation and local tissue metabolism, promotion of resorption and restoration of function. An even more important effect of suitable local heat application is that of the relief of pain, the symptom which is the most bothersome and most depressing, next to the stiffness and limitation of motion.

For simple yet efficient heat application in the home and in the office, *infra-red* and *luminous heat generators* mounted on suitable stands are now universally preferred, and have largely replaced the former cumbersome dry baking apparatus and light boxes. The penetrating effect of the luminous heat is somewhat deeper than that of *infra-red* radiation. For home treatments patients should be instructed to use these appliances

for one-half hour two or three times a day over the affected joints. Such heating should be followed by gentle stroking massage applied by a well-instructed member of the household. Well-planned home treatments help to keep patients comfortable and allow the bridging of the time between office visits.

*Diathermy* has become recognized in recent years as an efficient form of deep heating. Clinical experience has shown that especially in cases of osteo-arthritis localized in one or two of the larger joints or in the spine, diathermy will do more for local relief of pain, promotion of resorption and restoration of function than any other physical measure; it also lends itself easily to a combination with other measures. In the so frequent bilateral knee involvement of the osteo-arthritic type in middle-aged women diathermy combined with suitable rest will give complete relief in the great majority of cases. In traumatic arthritis, diathermy followed by massage or the static wave current is likewise the line of first attack. In gonorrheal arthritis diathermy may serve for the eradication of the focus of infection in the genital tract as well as for the treatment of joint changes.

The newer method of *short-wave diathermy* has been shown to exert more penetrating heating effect and its technic is more simple; on the other hand its dosage regulation compared to diathermy is crude and there is a possibility of overheating deeper avascular structures. The clinical results with its application are the same as with diathermy.

*High frequency sparking* (known as the Oudin current) has a well-defined use for mild counterirritation in fairly sub-acute arthritis involving several joints, also in diffuse pain of neuritic character. It should be employed following external heat treatment. In painful involvement of small finger joints the hot-air douche, produced by an ordinary hot-air drier, affords usually a marked analgesic effect.

**Heliotherapy.**—The beneficial effect of both natural and artificial light treatment in cases of tuberculous arthritis are well known, and is explained almost entirely through the constitutional effects of the irradiation and of the other factors—elevation, mountain air, rest and relaxation. These factors also explain the good results in certain forms of chronic arthritis following sojourns in heliotherapy resorts. The rationale

of light therapy may be based on three considerations: first, the tonic effects of radiation, especially in patients with asthenic constitution and rheumatoid arthritis; second, the findings of many investigators that chemical, thermal and other "insults" of the skin provoke or increase the defensive power of the body partly by a direct effect on improving immunity and partly by stimulating the immunizing mechanism through the absorption of the products of tissue damage, for ultra-violet irradiation, causing a varying degree of dermatitis, acts like foreign protein therapy; third, the direct thermal effect of the infra-red rays.

**Galvanic Current and Ionization.**—The time-honored *galvanic current* offers a useful adjunct in treatment of chronic arthritis especially the atrophic type. It brings about prolonged hyperemia of the skin and has some effect on the deeper circulation by reflex or direct penetration. Good results have been reported in the local treatment of joints where fibrous tissue changes have taken place. For therapeutic efficiency it is important that as large amount of current as can be borne be applied for a sufficiently long time, at least one-half hour sessions.

*Ionization with vasodilating drugs* has been extensively employed in recent years. The rationale of this treatment is based on research work pointing to the close connection between disturbed peripheral circulation and arthritic conditions. These studies showed that in arthritis there is a tendency in the capillaries of the skin toward relatively empty vessels and a sluggish flow of blood. There is much less blood as a whole in fewer capillaries to be seen in many cases of arthritis than in normal persons. The circulation is often sluggish and interrupted and there is apt to be present a contrast between the venous and the arterial side.

Histamine and choline compounds are introduced through the polarity effect of the galvanic current—from the positive pole. They penetrate the deeper layers of the skin and exert local as well as systemic effects; acting as antagonists to atropine, they stimulate the parasympathetic nerves and dilate the peripheral vascular system. *Mecholyl* ionization has been found a useful palliative treatment in rheumatoid arthritis where other methods of physical therapy directed to the relief of the local condition failed. This method is especially ap-

plicable in affections of the joints of the hands and fingers. *Histamine* ionization brings about a more vigorous local reaction and seems to be preferable in rheumatic myositis and neuritis.

**Electrical Massage and Exercise.**—The *static wave current*—when static apparatus is available—offers the best effect of a gentle, pleasant molecular massage and “decongestion.” Whenever there is edema and marked stasis it can be reduced by the static wave current with less effort and trauma than hand massage. Static sparks applied around tense and spastic joints aid their mobilizing; patients usually feel markedly limbered up after a series of well-placed sparks.

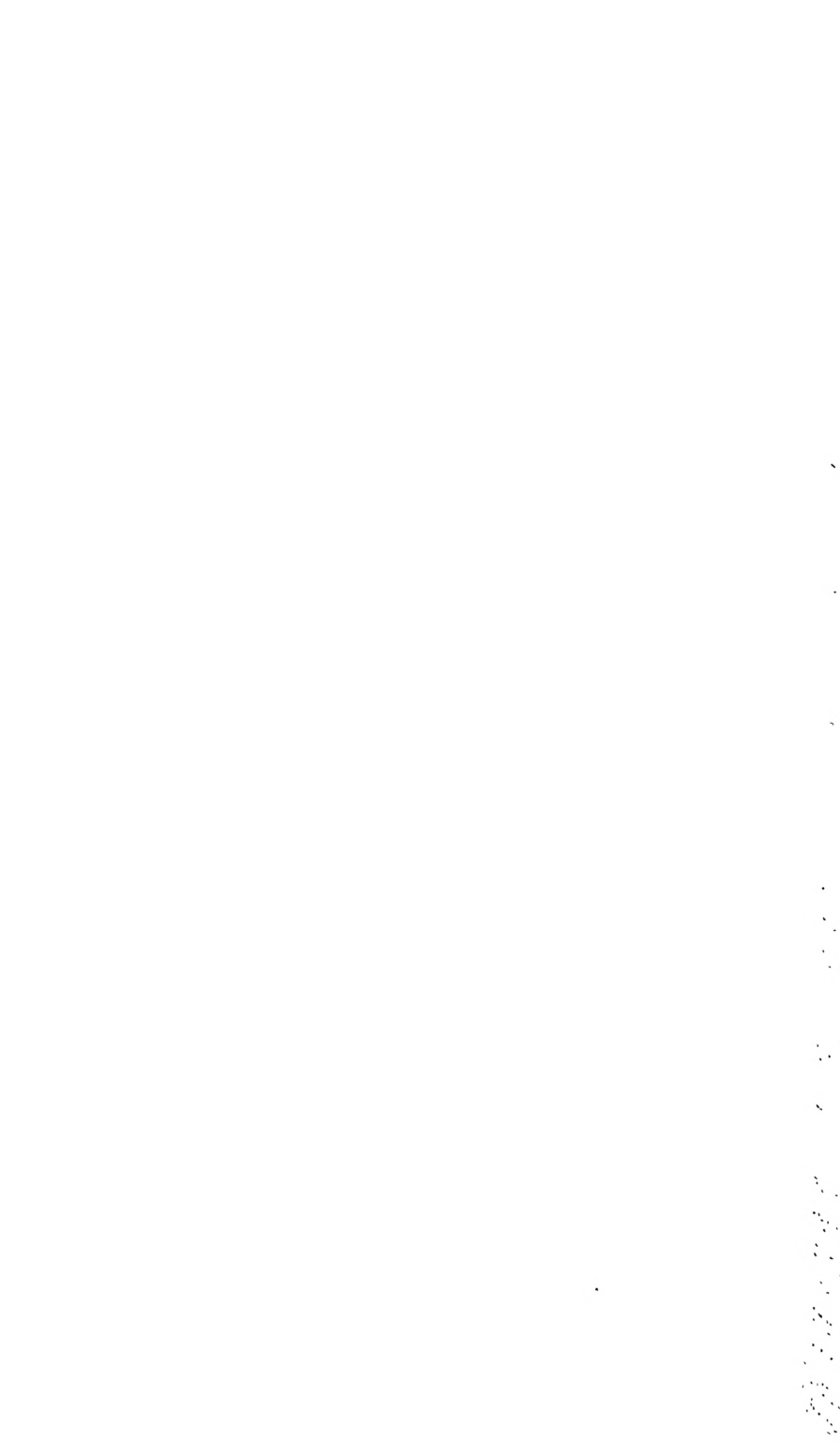
In visceroptosis and sluggish bowel activity of arthritic patients, exercise of the abdominal muscles by voluntary work or by a *low-tension wave current* (the surging faradic or interrupted sinusoidal) may be indicated. Its systematic application aims to improve the tone of the musculature, peristalsis, the venous return from the abdomen to the heart and also glandular function. Electrical exercise of the large muscles of the extremities may aid in maintaining the tone and in preventing atrophy so frequent in the later stages of arthritis. It has been shown that muscular contractions of this kind partake more of the nature of massage than of active exercises and have the advantage of making fewer demands upon the cooperation or energy of the patient than exercise does.

**Scheme of Treatment.**—The large number of electrical measures described constitute an invaluable aid in the constitutional therapy of chronic arthritis and are the mainstay of its local treatment. It is evident that all these measures must be employed in conjunction with a plan of general medical treatment. It must be emphasized again that in the routine management of arthritis one cannot separate electrical measures from other physical measures such as massage, exercise and the various forms of hydrotherapy. All these measures may be used in suitable combination or alternation. A change of methods from time to time is desirable because any form of stimulus employed over a long period of time will lose some of its effect. In the following brief description of the scheme of treatment in the principal types of chronic arthritis, therefore, all available physical measures have been taken into consideration.

1. *Osteo-arthritis*.—The average patient with osteo-arthritis is usually a well-nourished individual after middle age; in its etiology trauma, overuse or metabolic factors are the most frequent causative factors and not infection; the joint changes affect fewer and larger joints. Early cases of this type can be given almost complete relief by suitable physical measures in conjunction with suitable dietetic régime and regulation of habits. Diathermy to the joints combined with massage or the static wave current is usually quite effective. In advanced cases or cases affecting several joints a course of careful general heating may be indicated; this may be done in the form of a stay at a hot spa. In cases complicated by synovitis the static wave current is valuable.

2. *Rheumatoid Arthritis*.—This form of the disease occurs in younger persons usually in poor stage of nutrition. Infection may play a rôle in its onset and it affects, as a rule, many of the smaller joints. In this condition the entire range of available physical measures must be drawn upon to aid the general medical treatment. Mild general thermal treatment is indicated from the beginning to aid general circulation. Early heliotherapy, natural or artificial, is important for general tonic effects. Suitable exercises, general as well as local are to be instituted to correct posture and prevent deformities. For local treatment, especially at home, daily use of luminous or infra-red sources followed by gentle massage and active exercise is advisable. Ionization with vasodilating drugs is valuable in reducing swelling and pain in small joints which do not respond to mild thermal treatment.

3. *Gonorrheal Arthritis*.—A typical affection of one single joint is usual in this infectious form of arthritis; an attack on several joints occurs not too infrequently. The sovereign treatment consists of intense heating to the suspected focus of infection, the affected joints or to the entire body. In the painful acute stage joints usually can stand only mild continuous heating from radiant sources; diathermy at this stage is apt to bring about a severe local reaction. In the chronic stage, intense diathermy or short-wave diathermy locally applied to the joints will clear up many cases; in resistant cases and those affecting several joints, artificial fever therapy is indicated and is effective in a very large percentage of cases.



## CLINIC OF DR. NORMAN EDWIN TITUS

BEEKMAN STREET HOSPITAL

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### PHYSIOTHERAPY IN ARTHRITIS: HYDROTHERAPY

HYDROTHERAPY is a comforting and widely accessible form of conductive heat that has been used for the pains in arthritis since years before anything was known about the disease. Cures or spas, where hydrotherapy was the main form of treatment, have been relief-giving and utilized all over Europe since the time of the Romans. Mysterious powers have been claimed for different waters and it is barely possible that some of them, due to what is now known to be radio-activity, produce more effect than bland waters containing varying amounts of salts. The spas frequented by rheumatic patients depend largely upon their salt content for their accredited, varied effects. We know that these baths at European spas, combined with the regular régime, are beneficial for many cases of arthritis but it is a question what percentage of this benefit is derived from the water itself.

In the United States our few well-known cures, such as Hot Springs in Virginia, Hot Springs in Arkansas and Saratoga Springs, are too near the telephone for patients to relax completely. When they really wish to take treatment, they prefer to go abroad, both for the trip and the seriousness of the atmosphere which makes them live up to the prescribed régime. It is to be regretted that the American cures are more places for social gatherings than serious medical treatment.

Some of the cures combine their water baths, which may be included in the term "hydrotherapy," with baths of either radio-active or ordinary mud. These mud baths are generally taken in tubs and are followed by sprays of water to clean it off. Mud from the northern part of Italy is obtained from the

bottom of crater lakes and hence has a high content of volcanic ash, and because of its adhesiveness, can be used for mud packs. More radio-activity is accredited to this kind of mud than to others. Be that as it may, it is a moot question how much benefit is derived from any radio-activity either in mud or water. But this quality has a great sales attraction for the different spas.

The hydrotherapy technic used at these cures is immersion for various lengths of time, with or without manipulation. In England it is usual to give exercises to a patient while immersed in the water and under-water douches are administered with the stream directed at the affected joint. Exercises under water undoubtedly are more beneficial than those on land because the limb floats and less muscular effort is needed. This has been brought out since attention has been directed to hydrogymnastics for the treatment of the paralytic. A great deal of work is being done on paralytics and it is hoped that eventually it will come about in this country that arthritics receive the benefit of hydrogymnastics. This kind of exercise in warm water helps to relieve the pain due to muscle spasticity.

For the treatment of arthritis of the joints of the feet, ankle, hand and wrist, the whirlpool bath is particularly sedative. The original whirlpool bath was designed during the World War. In this, water was forced through a nozzle under pressure into a cylindrical tank and air was sucked in with it, making a strong stream of bubbles and giving a very delicate massage. Agitated water can be tolerated by the patient at a higher temperature than if it were still. The whirlpool bath also has been found to cause a more prolonged hyperemia of an extremity than any other method, including electrical treatments.

The whirlpool bath, hydrogymnastics and the under-water douche without air are applicable for direct effect on specific joints. They are combined, as is being done by Currence in New York. He uses a tank for hydrogymnastics and with the Titus whirlpool agitator directs a stream of water toward the affected joint while exercises are given.

Arthritis is a constitutional as well as local condition and constitutional effects are easily obtained by all forms of hydrotherapy. Not only the general immersion baths are employed but patients frequently are put in foam or bubble baths. A

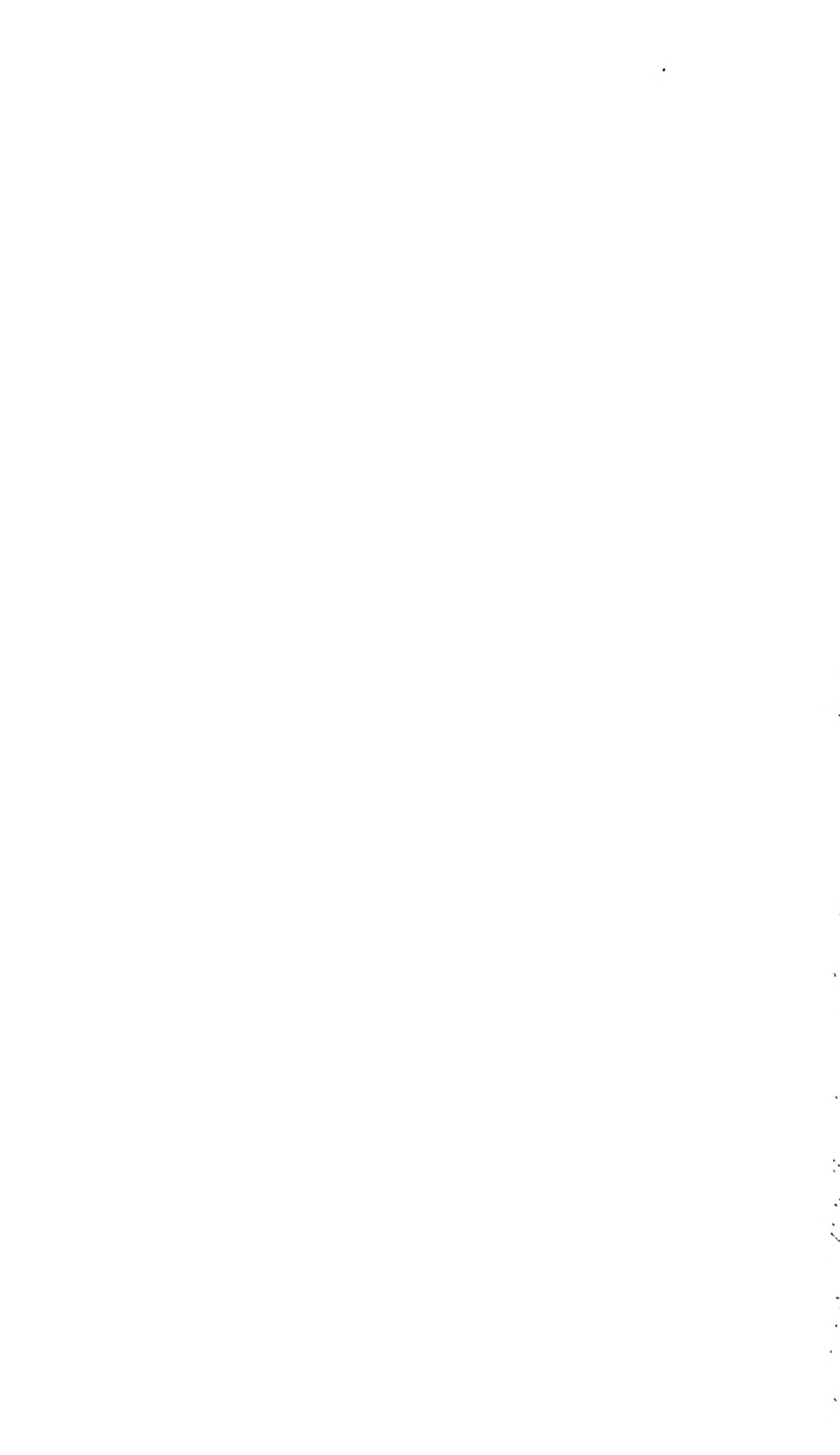


foam bath, as the name implies, is a tub full of foam. This is generated by mixing a few drachms of a saponin solution with about 3 inches of water in the bottom of a tub. A long frame with perforated tubes in it is immersed in this water and air or oxygen are forced through this mixture to form the foam. With this apparatus a tub can be filled with foam in from ten to fifteen minutes. The patient then gets into the tub and is completely covered by the foam, which restricts the radiation of the heat from the entire body. The foam itself is also hot and great perspiration is induced with the natural elimination of toxins. These baths have a very sedative effect upon patients, especially if they are of the nervous type.

With the same rack placed in an ordinary bath tub filled with water, air can be forced up through the water, giving a general massage with small bubbles to a patient's entire body. These bubbles may be of ordinary air from a pump, carbon dioxide or oxygen from tanks.

Hydrotherapy as an adjunct to the treatment of arthritis has the great disadvantage that it cannot be given conveniently in a doctor's office or in a patient's home. It requires hospital equipment and a real department in which everything is available, as well as hydrotherapy.

Hydrogymnastics should be preceded by applications of convulsive heat, either radiant or electrical, and tonic baths are best accompanied by ultraviolet light baths. Massage in or out of water should also be given. The use of a single modality in physical therapy is not rational treatment and hydrotherapy, through stimulation of the circulation, is more symptomatic than anything else.



## CLINIC OF DR. IRVINE H. PAGE

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#### THE GENESIS AND TREATMENT OF EDEMA IN BRIGHT'S DISEASE

PHYSICIANS in the eighteenth century knew that dropsy resulted from a number of causes. Apparently Blackall and Bright were the first to recognize its association with morbid changes in the kidneys. Bright's associate Dr. Bostock was, indeed, aware of the fact that the specific gravity of the serum was sharply reduced in certain patients in whom dropsy was observed.<sup>1</sup> He associated the low specific gravity correctly with loss of plasma albumin in the urine; but he did not realize that the dropsy was often causally related to the deficit of plasma proteins. It remained for Starling<sup>2</sup> to propose that the osmotic attraction for water by the plasma proteins was a force of great importance in the maintenance of exchange of fluid between the blood stream and the interstitial fluids. Starling believed that the exchange of fluid between the capillary blood and the tissues was controlled by at least two opposing forces, namely, the hydrostatic pressure within the capillaries which tended to force fluid out of them and the osmotic attraction of the plasma proteins, which tended to draw fluid into the blood stream. That these factors are important in the edema in nephrosis and nephritis was pointed out by Epstein<sup>3</sup> and Govaerts.<sup>4</sup> Thus it is that hypoproteinemia has come to be recognized as one of the chief causes of edema occurring in chronic nephritis and nephrosis. Other types of edema also occur, especially in the acute onset and during the terminal stage of nephritis. The typical "nephritic" or "nephrotic" edema, however, is associated regularly with, and in large part due to, plasma protein deficit.

## THE NON-NEPHROTIC EDEMA OF THE ONSET OF ACUTE NEPHRITIS

This edema occurs *before* plasma protein deficit develops. It exhibits characteristic predilection for the face and especially the eyelids. The ankles, feet, hands, scrotum and labia are usually involved less frequently and in the order named. It appears that this type of edema is due to increase in permeability of the capillary wall which allows the escape of protein into subcutaneous tissues. This extravascular protein exerts enough osmotic attraction to draw water from the blood plasma in sufficient quantities to be recognized as excess fluid in the tissues. Edema fluid from such patients, unlike that from patients with nephrotic edema, is rich in protein. The escape of proteins from the circulating plasma is evidence that the permeability of the capillaries is increased.

The cause of the increase in capillary permeability is unknown. Most observers have suggested that it is toxic in origin chiefly for two reasons. It occurs usually closely associated with infection or an episode involving anaphylaxis. Its appearance resembles edema produced by injection of toxic substances.

The non-nephrotic edema of acute nephritis is transient, seldom lasting more than a few days or weeks. It causes the patient little discomfort and requires no treatment. However, it is important to recognize it chiefly for two reasons. It calls attention to a serious disease and it suggests that blood vessels other than those of the kidneys are involved in the morbid process.

Often this edema is so transient or mild that it is not noticed by the patient. It may be present in the morning when the patient awakes and disappear as the day progresses. It is often dismissed by him as due to gastro-intestinal upset, fatigue or alcohol. The initial stage of Bright's disease is often therefore overlooked and attention is called to the disease only after it has entered the chronic stage. Thus the non-nephrotic edema of acute nephritis may be viewed as an important danger signal, which in itself needs no treatment, but which urgently demands that the underlying disease of the kidneys and blood vessels receive attention.

## NEPHROTIC EDEMA

Edema due chiefly to abnormally low plasma proteins, so-called "nephrotic edema," occurs during the course of both chronic hematuric nephritis and during nephrosis. Often the differential diagnosis between them is difficult or impossible. Hypoproteinemic edema in the majority of adult patients, however, is associated with hemorrhagic nephritis.

Nephrotic edema is usually obvious and obstinate. In the so-called "preedematous stage" the skin feel doughy and lacks normal elasticity. When frank edema appears, it affects those parts of the body most subjected to the force of gravity. If the patient is up it will be most conspicuous in the ankles and legs, while if bedridden, the sacrum, scrotum, labia, back, face and arms are also involved. In some cases ascites is prominent.

As the terminal phase of the disease approaches, the nephrotic edema may continue, but often the plasma proteins rise spontaneously and the edema disappears. This terminal "dry phase" is sometimes followed by edema due to cardiac failure.

**Causes of Nephrotic Edema.**—A number of different factors are responsible for the occurrence of nephrotic edema, the better understood and possibly more important among these being: (1) hypoproteinemia with consequent loss of osmotic attraction of the plasma for water, (2) the hydropigenous effects of salt in the tissues. Most evidence<sup>5</sup> does not support the belief that the ionic excretory power of the kidneys in nephrotic patients is qualitatively different from kidneys of normal persons, although the tissues of edematous patients on a salt-poor diet appear to retain more salt and consequently water than do normal persons on the same régime. Studies on the drainage of fluid by way of the lymphatics away from the edematous areas show that it is very active.<sup>6</sup> This is in marked contrast to the stagnant lymphatic drainage in cardiac edema.

Deficit of plasma protein, as has been said, is one of the most important causes of nephrotic edema.<sup>7</sup> In normal human beings the total plasma protein content is about 7 Gm., the albumin 4.5 and the globulin 2.5, per 100 cc. of plasma, and the specific gravity is 1.027. But if the total plasma proteins in an adult fall below 5 Gm., the albumin below 2 Gm., and the specific gravity below 1.023, edema usually appears. When

the total protein is between 4 and 5.5 Gm. and the albumin between 2 and 3 Gm., edema may or may not be present, often depending on whether salt restriction and rest in bed are prescribed. In children and occasionally in adults somewhat less plasma protein may be required to prevent the appearance of edema.

When hypoproteinemia occurs in Bright's disease it is chiefly the albumin fraction in the plasma that is lowered. Since the osmotic activity of the albumin is about three times as great, per gram, as the activity of globulin, the effect on the edema-preventing colloid osmotic activity is greater than if the globulin were lost.

Important as hypoproteinemia is in the genesis of nephrotic edema, other, as yet unknown factors, also influence the fluid retention. Edema may disappear without any rise in the depressed plasma protein level.<sup>8</sup> This is often observed following fever and seems to occur in children more commonly than in adults. Furthermore, several patients have been described in medical literature in whom hypoproteinemia has occurred without the simultaneous appearance of edema. Edema has been observed to disappear in patients receiving high protein, low salt diets, even when the plasma colloid osmotic pressure is below the level at which edema is usually present. But the tendency to edema still appears to remain in most cases until the plasma protein concentrations increase above their critical levels.

**Causes of Hypoproteinemia.**—Since the edema fluid contains only very small amounts of protein, there is little reason to believe that the permeability of the capillary walls is more than slightly increased in the edema of *chronic* nephritis.

The causes of the lowered plasma proteins must be searched for elsewhere. The most obvious of these is loss of protein in the urine. Many patients lose as much as 25 Gm. of protein a day. It has been observed that when protein excretion exceeds 6 Gm. a day nephrotic edema usually occurs, although this correlation is only approximate. Protein loss in the urine places a heavy demand on the synthetic power of the body and constitutes probably the most important cause of hypoproteinemia in Bright's disease.

A second important cause of plasma protein deficit is a diet

low in protein content. This was illustrated during the war by the appearance of edema among the population of countries where protein foods were sharply curtailed. Such nutritional edema has also been produced in dogs fed low protein diets.

The protein lost in the urine must obviously be replaced either from the tissues or from the constituents of the diet. It is common clinical experience that Bright's disease is a wasting disease.<sup>9</sup> Especially when edema disappears is it evident that the body tissues have been drawn upon and seriously depleted. Malnutrition as well as Bright's disease produces hypoproteinemia especially in the albumin fraction; hence malnutrition alone must be reckoned as an important factor in the genesis of hypoproteinemia.<sup>10</sup>

It is possible that a third cause of hypoproteinemia is inability of the body to synthesize sufficient protein to balance the loss in the urine. Protein intake may be adequate yet the loss of protein so great that the body appears to be unable to replace it fast enough. Sometimes, however, a patient is seen whose proteinuria disappears, and who receives an adequate protein diet, and yet whose plasma proteins do not rise to a normal level. Whether this is due to impaired ability to synthesize plasma protein or to change in the mechanism which controls the level of proteins in the plasma is not known. It appears unlikely that impaired ability to synthesize plasma proteins is common in Bright's disease since disappearance of proteinuria is usually accompanied by a rise in them. Furthermore during the terminal stage of the disease, when this power could be expected to be most seriously impaired, the plasma proteins often rise and edema disappears unless complicated by coexistent edema of cardiac origin.

#### SALT AS A FACTOR IN THE PRODUCTION OF NEPHROTIC EDEMA

It has been known for years that the intake of salt influences the appearance and extent of nephrotic edema. Water cannot be retained without an equivalent amount of salt, nor salt without an equivalent amount of water.<sup>11, 12</sup> Even in normal persons amounts of salt of the order of 35 to 40 Gm. in a day will produce edema. But in subjects with edema and decreased colloid osmotic pressure of the blood there is a magnified tendency to retain salt along with sufficient water to form

physiologic saline solution. Salt retention does not of itself usually produce edema, but associated with hypoproteinemia it greatly increases it. The sodium and not the chloride ion appears responsible for the hydropigenous effect of salt. Potassium salts, on the contrary, have no hydropigenous action.

#### DETERMINATION OF PLASMA PROTEIN

Proper understanding of the cause and treatment of edema occurring during Bright's disease is so dependent on knowledge of the amount of proteins in the plasma that it appears useful to present a simple bedside method for their indirect estimation.<sup>13</sup> The method now described ascertains merely whether the specific gravity of the plasma is above or below the critical edema level, 1.0235. The blood is mixed with 1 mg. of heparin per cubic centimeter, or with not more than 2 or 3 mg. of oxalate, and is centrifuged. A drop of the plasma is let fall about 2 cm. from a pipe into a tube of organic fluid having the density 1.0235. For such fluid one may use pure phenyl fluoride,  $C_6H_5F$ , or a mixture of 1 volume of xylene with 2.06 volumes of phenyl chloride,  $C_6H_5Cl$ . If the plasma is sufficiently rich in protein to prevent hypoproteinemic edema, the drop of plasma will sink to the bottom. In contrast, the drop of plasma from a nephrotic subject will rise to the surface of the organic fluid. From the rapidity with which the drop falls or rises one can estimate roughly whether the specific gravity is near the critical level 1.0235 (very slow rise or fall), is near the normal 1.027 (rapid fall), or near the low extreme of nephrotic hypoproteinuria (1.019) (rapid rise to surface).

#### TREATMENT OF NEPHROTIC EDEMA

Since body tissues are wasted by the continuous loss of protein in the urine, one of the first objects of treatment of nephrotic edema is to replace this loss. This can be done only by generous feeding of protein.

In the past, protein feeding in nephritis has been guided by theoretical conceptions which in the light of more complete data appear to be incorrect. Impressed by the fact that end-products of protein metabolism, especially urea, were not adequately cleared from the blood by damaged kidneys, physicians



reduced protein in the diet hoping thereby to reduce the work of the kidneys. It was believed, further, that urea or other products of protein metabolism might in themselves be toxic when increased in amount in the blood.

Recent evidence from a number of clinics,<sup>11, 14, 15, 16</sup> however, has shown that fairly generous amounts of protein in the diet do not appear to intensify the morbid process in the kidneys as measured by the usual tests of renal efficiency. On the other hand, data are insufficient to decide whether diets containing 80 to 100 Gm. of protein hasten or retard progress of the disease toward its fatal termination.

It is now clearly established that definite benefits to tissue nutrition, normal water balance, and general strength, may result from avoiding low protein diets and allowing from 80 to 100 Gm. of protein in a normal, well-balanced diet with adequate amounts of vitamins. Shift from low to higher protein diets causes protein storage in the tissues of the patient. This diet aids in combating the wasting and malnutrition, a prominent sign of the disease, and helps to increase plasma proteins and consequently to decrease edema. This happy result may change the entire outlook for the patient. In place of being bedridden from edema and malnutrition the patient often resumes nearly normal activities. It is especially desirable that children receive adequate amounts of protein in their diet to avoid interference with normal growth.

Marked variability is shown by patients in their response to protein feeding. Those that have consumed ordinary amounts of protein may not show benefit from its increase in the diet until two months or more. The diet should not, therefore, be abandoned after a few weeks' trial. By no means do all patients respond by rise in plasma proteins when protein is increased in the diet. If the individual is already well nourished and if excretion of protein in the urine does not exceed 6 Gm., the protein in the diet may be varied within relatively wide limits without significantly affecting the level of plasma proteins.

In this clinic a diet containing from 80 to 100 Gm. of protein has been observed to be adequate for an adult losing less than 10 Gm. of protein a day in the urine. Usually there is little to be gained by using higher protein intake and much to

lose as digestive disturbances may readily occur. Children, however, consume diets containing about 3 Gm. of protein per kilogram of body weight with apparent benefit.<sup>17</sup> The ratio of animal proteins (meat, eggs, milk, casein) to vegetable protein given in the diet in this clinic is about 2 to 1. Casein\* taken with milk is a cheap and convenient form in which to administer it but skimmed milk powder is better tolerated by children.

### SALT RESTRICTION DESIRABLE

Salt restriction is imperative in the treatment of nephrotic edema. The ordinary diet contains 10 Gm. or more of salt but restriction to about one fourth of this amount is compatible with perfect health. In adult patients with nephrotic edema it is desirable that not more than 2 to 3 Gm. of salt be allowed. It should be remembered, however, that as the disease approaches the terminal stage, *inability* to retain sodium chloride develops, several grams of salt per day may be excreted even on a salt-free diet, and hypochloremia may occur. This appears in some patients to hasten the onset of uremia. The need for salt restriction often disappears along with the plasma protein deficit during this stage. In children the restriction of salt is of paramount importance. Less than 1 Gm. a day in the diet should be allowed. There is no retardation of growth and development with such restriction.<sup>17</sup>

### PREPARATION OF CASEIN

The following recipes have been prepared by Miss G. Drew.

*Casein Preparation No. 1.*—Milk or water 150 to 200 cc., casein 15 to 35 Gm.; mix together slowly, stirring until smooth.

*Casein Preparation No. 2.*—Cocoa 2 Gm., sugar 5 to 10 Gm., water 25 cc., milk 175 cc., casein 15 to 35 Gm. Scald milk and mix cocoa, sugar and water, cook for five minutes and add to scalded milk. Cool and mix with casein slowly, stirring until smooth.

*Casein Preparation No. 3.*—Milk 165 cc., egg 35 Gm., sugar 5 to 10 Gm., vanilla to flavor, casein 15 to 35 Gm. Make

\* An edible casein powder prepared by the Casein Manufacturing Company, 350 Madison Avenue, New York, may be useful in enriching the protein content of diets for adults. It is cheaper than meat protein.

eggnog with milk, egg, sugar and vanilla. Mix with casein slowly and stir until smooth.

Liquid ingredients may be either warm or cold, but never hot when mixing with casein.

Salt-poor diets may be best prepared merely by avoiding foods to which salt has been added. No naturally occurring foods contain important amounts of salt, except those in which sea water is mixed (*e. g.*, clam and oyster juice). Salt substitutes are ordinarily not necessary and often impart an unappetizing taste to the food. The palatability of food may be increased by use of flavoring with onion, lemon juice, vinegar, mustard, pepper, nutmeg, etc.

#### WATER RESTRICTION UNDESIRABLE

Water restriction is unnecessary. Patients with nephrotic edema will not retain water unless with it they retain a physiologically equivalent amount of sodium salts. Even large volumes of water given without salt are excreted by these patients without difficulty; in fact, the diuresis may hasten salt excretion and reduction of edema. Limitation of water produces unnecessary and useless suffering from thirst, and reduces urine output to volumes below that at which renal excretion of solids is most efficient (*e. g.*, with a urine volume of 0.5 cc. per minute urea is excreted only half as rapidly as with a volume of 2 cc. per minute). Only when cardiac failure occurs, and it is rare in nephrosis or the nephrotic stage of Bright's disease, is water restriction justified.

#### SURGICAL TREATMENT

If edema fails to disappear after a diet adequate in proteins and vitamins and low in salt has been given for four months or more and bed rest enforced, denervation of the kidneys may be considered. As this operation has only been employed for this purpose recently we do not yet know the physiologic changes by which it diminishes the tendency to edema.<sup>18</sup> Denervation of one kidney may be as successful as denervation of both. The operation need have no mortality. It may be performed under local anesthesia though this appears to be rarely necessary. If the urea clearance is below 20 per cent

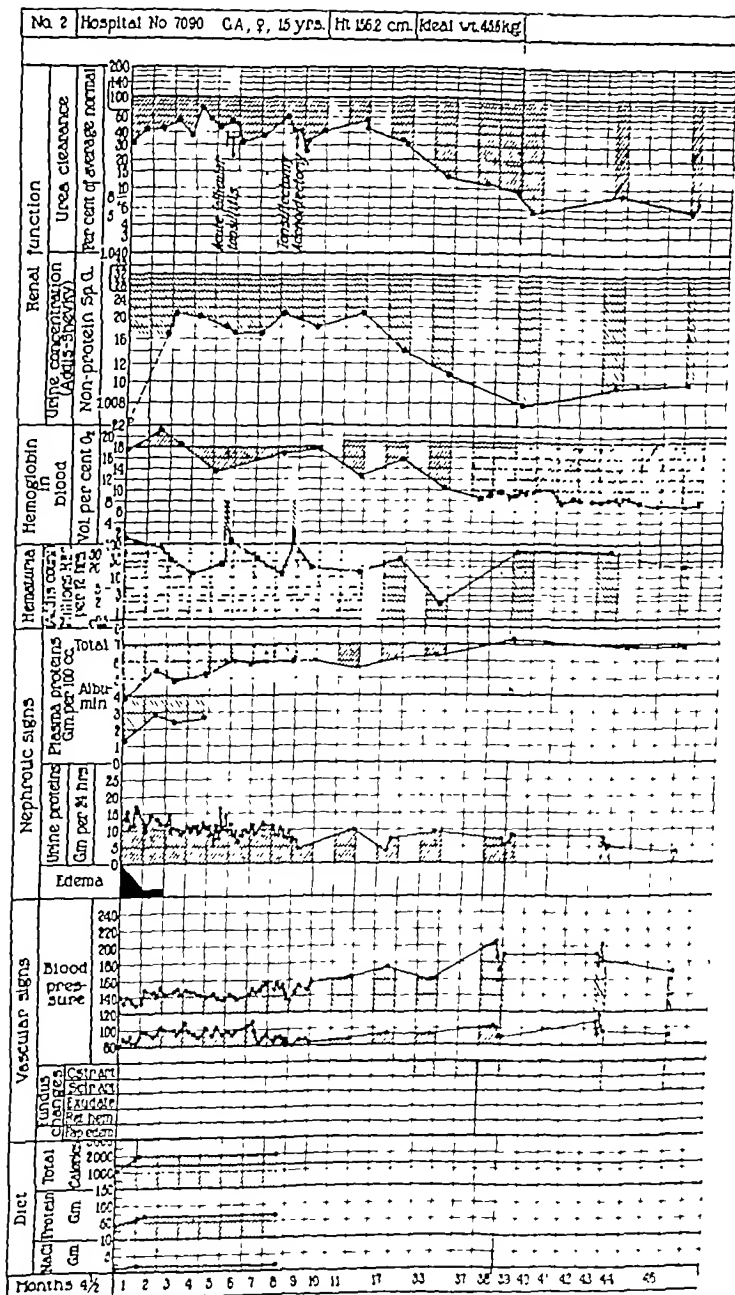


Fig. 137.—Example of a patient suffering from Bright's disease who had consumed an inadequate diet. Edema was intense, but within two months had subsided when a diet containing 75 Gm of protein and 2.5 Gm of salt was given. Associated with the loss of edema was a rise in plasma proteins but no significant change in the output of protein in the urine.

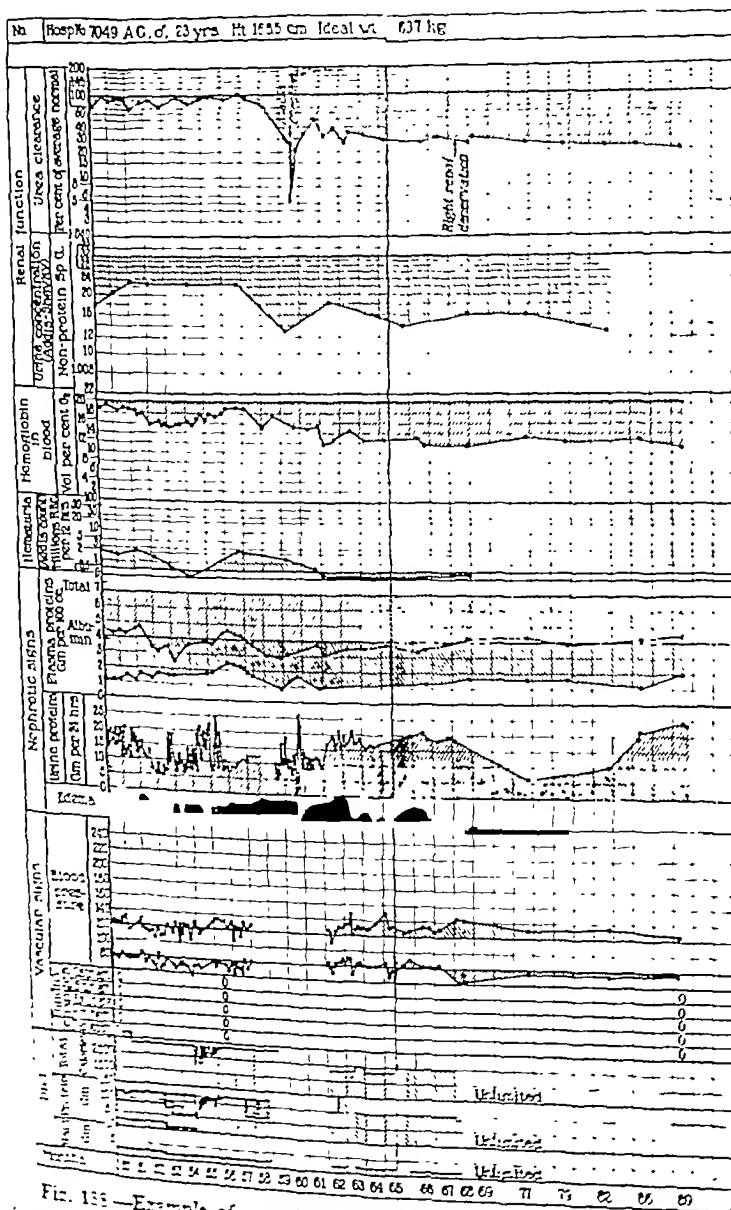


FIG. 135.—Example of a patient in the nephrotic stage of chronic Bright's disease. Edema and ascites had been his most persistent and disabling sign. He was free of them only for short periods. Following renal denervation he was free for two and one-half years in spite of consumption of 1000 mg. of salts. No adequate explanation has been found for this.

of normal there is no justification for performing it because, except insofar as it betters the clinical condition of the patient, it does not affect the renal efficiency as judged by urea clearance or ability to concentrate urine.

For several months after operation protein in the urine may be sharply diminished and a moderate rise in plasma protein may occur. In some patients this persists but in others return to the preoperative rate of excretion of protein occurs. Denervation does not lead to persistent polyuria in our experience. Apparently almost independent of the plasma protein level the edema may completely disappear and salt may be added to the diet without reappearance of edema. As a result of disappearance of the edema the clinical condition of the patient is greatly improved. A favorable result does not always occur, but there have been no observations made on these patients which indicate that harm has been done.

#### MEDICINAL TREATMENT

**Diuretics.**—Opinion differs as to the desirability of employing diuretics in the treatment of nephrotic edema. It is generally agreed that they are not as useful as in the treatment of cardiac edema.<sup>19, 20</sup> After trying the various organic and mercurial diuretics, and the acid-forming salts, such as ammonium chloride and nitrate, we have in the Rockefeller Hospital practically abandoned all of them in treatment of nephrotic edema, except urea. Large doses, 30 to 60 Gm. per day, are required, and can be continued for prolonged periods. They may assist in keeping edema within tolerable limits, and in obviating the necessity of abdominal tapping. The effect of the urea lasts only as long as the administration is continued. The hydropigenous factor of the disease does not disappear until the plasma proteins rise above the critical concentration.

**Blood Transfusion and Acacia.**—Attempts have been made to increase the colloid osmotic pressure of the plasma by blood transfusion or administration of colloid such as gum acacia. Actually the amount of plasma protein added by a single blood transfusion is not great (25 to 35 Gm.) and may be quickly lost in the urine. Intravenous injection of pure gum acacia (30 Gm. in 300 cc. of water) may initiate diuresis

Occasionally during administration of acacia a shocklike syndrome appears. We have also seen a serious reduction of renal efficiency follow acacia injection. The acacia is said to localize eventually in the liver, and may damage that organ. We have entirely abandoned the use of acacia as a diuretic in nephrosis.

### CARDIAC EDEMA

Edema due to cardiac decompensation may occur at any stage of Bright's disease. It is, however, rare during the acute and intermediate chronic stage. During the terminal stage it is a usual occurrence and may be chiefly responsible for the edema or may add to the edema already present due to hypoproteinemia.

Cardiac edema is due chiefly to increased hydrostatic pressure in the capillary bed. Increase in the permeability of the capillary walls due to reduction in blood flow and its attendant tissue anoxemia also plays a part. As a result, some protein is lost into the tissues. The edema fluid contains more protein than edema fluid from a nephrotic but less than that from an acute nephritic.

The signs and symptoms of cardiac failure always accompany cardiac edema. Furthermore the plasma protein content is only slightly lowered in comparison to nephrotic edema in which 5 Gm. or less is present.

**Treatment of Cardiac Edema in Bright's Disease.**—It is of first importance to try to restore the heart to a state of compensation since failure of the heart is responsible for the edema. In patients suffering from Bright's disease, methods for restoring the power of the heart do not differ from those employed in usual practice. Salt restriction is also a necessary part of the treatment. Just as in nephrotic edema the hydropigenous properties of sodium salts exhibit themselves. Since the plasma proteins are not necessarily significantly reduced in cardiac edema it is neither necessary nor desirable to offer the patient more than small amounts of them. Indeed the total intake of food should be somewhat reduced to about 1500 to 1800 calories. When cardiac edema appears the patient is usually so ill that it is inadvisable to force any special diet. The physician may count himself fortunate if the

patient does not lose his appetite entirely and begin vomiting. If pure cardiac edema were present without impending uremia it would be desirable to restrict the fluid intake to about 1000 cc., but it is rare that one sees this. More usual is the combination of cardiac and nephrotic edema in a patient whose renal efficiency is seriously impaired. A middle ground must therefore be chosen. Adequate digitalization must be immediately secured. The diet must be appetizing and not greater in caloric value than 1500 to 1800 calories. It must contain not more than 2 to 5 Gm. of salt provided marked polyuria is not present, in which case 10 Gm. of salt should be allowed. Complete bed rest is essential. Fluid restriction is usually not possible or desirable. While it might, on theoretical grounds, aid in checking more edema formation the good results are not balanced by the bad. Unless a good flow of urine is maintained the clearing of the blood of waste products by the damaged kidneys is not efficient. While diuretics find their greatest field of usefulness in treatment of pure cardiac edema they are of little value when the kidneys are hopelessly damaged. The few remaining glomeruli and tubules are probably already working at maximum capacity and the tubules are unable to reabsorb water. Diuretics can only harm such a kidney. Thus the treatment of edema during the terminal phase of Bright's disease often becomes a compromise between the procedures which are desirable in the treatment of edemas of cardiac and nephrotic origin.

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## CLINIC OF DR. I. S. WECHSLER

### THE MONTEFIORE HOSPITAL

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#### ON THE DIFFERENTIAL DIAGNOSIS OF NEUROSES FROM ORGANIC DISEASES

ONE of the fears which beset every practitioner is that of making erroneous diagnoses of psychoneurosis in the presence of organic diseases. Every physician is occasionally chagrined to find that what he treated as a hysteria or neurasthenia turned out to be a malignancy, a pernicious anemia or leukemia, or a tumor of the brain. While the dangers involved are not nearly so great in the discovery that what passed for gallbladder disease actually was a psychoneurosis, the waste is no less deplorable and the chagrin no less keen. Naturally these errors of diagnosis decrease as knowledge and experience grow, but the perplexities of the conscientious physician usually increase as his knowledge widens.

To allay the fears and prevent the diagnostic errors a number of practical and theoretical criteria are generally laid down, but it may be confessed that they often serve least when the difficulties are greatest. None the less a few general principles may serve to minimize the errors even though they may not eliminate them altogether. It is needless to state that the best defense against mistaken diagnoses is a sound knowledge of medicine and the avoidance of snap judgment even in what appears to be a simple case. Errors of omission are generally at the root of most diagnostic mistakes. This does not mean to say that one should make it a hard and fast rule to "work up" every case with all sorts of tests and examinations when sound clinical judgment counsels against it. Very often insight and understanding, and particularly a careful history, will show the irrelevancy and even the harm of overworking the labora-

tory investigations; but if one is not to err it is generally wiser to do more rather than less through studies.

Perhaps the best general rule, worth repeating though trite by now, is never to make the diagnosis of psychoneurosis by exclusion alone. The fact that no organic signs are present obviously does not mean that there is no organic disease. Naturally their presence speaks for organic conditions, although they do not exclude a neurosis since the two may coexist. But it is well to adhere to the principle that no diagnosis of anxiety or conversion hysteria or neurasthenia or compulsion neurosis should be made unless by means of a thorough history one discovers some psychogenic factors. This may not be easy in unintelligent or uncooperative patients but even in them investigation may repay the effort by uncovering psychic causes if not complex mental mechanisms. In the case of neuroses it is a wise principle to study each case individually and intensively, not to overemphasize isolated signs and symptoms, to study the history, the precipitating factors, the general mental make-up and type of reaction, and evaluate carefully the whole clinical picture.

Another general rule worth adhering to is to make a thorough physical examination even when the diagnosis of hysteria is fairly evident. Not only is this an excellent therapeutic measure, but it may serve to reveal the presence of organic disease when least expected. While a neurotic generally overemphasizes even minor physical complaints, the psychic symptoms may sometimes obscure very important ones. It is also well to reexamine the patient from time to time. Many psychoanalysts feel that it is contrary to good psychotherapeutic practice to make physical examinations in the course of treatment because of the neurotic tendency to seek refuge in somatic complaints and thus avoid the "disgrace" of psychic causes. There is much truth to this, but enough instances abound in which oversight led to rather tragic errors, so that this view need not be taken too seriously. In any case even a neurotic may develop organic disease. A few simple examples will illustrate this.

A young woman of definite hysterical make-up kept bringing an infinite variety of complaints every time she came to the clinic. Among them were

pains in the chest and shortness of breath. All of them were colored by anxiety which was invariably put down as hysterical. Because there was also a history of mild asthmatic attacks and frequent minor colds little attention was paid to the shortness of breath. As a matter of fact it never really amounted to true dyspnea. The need of expediting work in the clinic was another reason for paying scant attention to the lengthy complaints. One day she complained more insistently of her dyspnea and again was sent away with a placebo and the instructions to return the following week. She came back two days later. This time the chest was examined and a large amount of fluid discovered.

A middle-aged man of forty came to the office with a series of complaints which stamped him as a confirmed neurasthenic. He had indulged in self-gratification since adolescence and been impotent all his married life. Mutual frustration over the years and economic difficulties led to marital squabbles which caused and intensified a variety of neurotic symptoms. Among them were headaches and fatigue and lack of interest, which had increased of late. He was treated for years by numerous physicians and finally came to the neurologist. The examination was negative except for bitemporal hemianopsia and beginning pallor of the optic disks. Naturally the suspicion of pituitary tumor arose despite the neurasthenic syndrome. An x-ray of the sella amply confirmed the diagnosis and a successful operation proved it. Incidentally, most of the neurasthenic symptoms cleared up. Whether the pituitary tumor was the cause of the neurosis or developed in the course of it is a fine question worthy of discussion, but the relevant point is that only a careful examination could have served to make the diagnosis. It is understandable how the long history and the absence of so-called "pituitary" symptoms of polyuria, polydipsia, etc., should fail to arouse suspicions and how the diagnosis of neurasthenia should have been maintained for years, but the error of omission still remains culpable.

It is an old clinical observation that psychogenic disorders may simulate almost every organic disease, and it is equally true that many organic conditions can for a long time mask as neuroses. The old adage that one who knows syphilis knows medicine may be paraphrased to read that one who knows the protean manifestations of hysteria knows the practice of medicine. There is no doubt that much skill, art, knowledge and understanding are necessary for the diagnoses of the neuroses, and in no branch does neglect of general medicine entail more danger to one's reputation or peril to one's patients than in the field of neurology.

An extremely practical rule is not to make a diagnosis of hysteria or other neurosis, or at least exercise great caution, in an individual past forty who has not previously shown out-

spoken neurotic tendencies. It is a fact that most neuroses trace back to early life, and in practically every case one can elicit a history of some neurotic manifestations. The neurosis may blossom forth in adult life, but the soil has long been prepared in adolescence or childhood. The caution is particularly necessary in the case of a neurasthenic syndrome which comes on late in life in a person who has not been a masturbator or one who has not been impotent or never suffered from lack of energy or ambition. In such cases one should rather think of early general paresis, Addison's disease, pernicious anemia, tumor of the brain, malignancy, cerebral arteriosclerosis or some other at first obscure organic disorder. More simple medical conditions occasionally mask under neurotic façades, as the following case will illustrate.

A lawyer of forty-five was referred by his attending physician because of nervousness which had lasted for six months and been precipitated by severe illness in the family. Among the symptoms were sleeplessness, anxiety, tremor, restlessness, and inability to work. Inquiry into the history and personality of the patient revealed a very stable individual who had never been ill. He was happily married, his sex life was normal, his economic condition good, his social relations excellent. The family illness, which was quite disturbing when it happened, fortunately turned out well. It became clear that here was no neurotic soil in which neuroses grow, and yet the picture was that of a neurosis which refused to yield to treatment. The only physical signs present were slight tremor of the extended fingers and an accelerated pulse. Despite the absence of other signs and symptoms of hyperthyroidism the suspicion of its existence, strengthened by what appeared to be substernal dulness, was expressed, and a basal metabolism study as well as x-ray of the chest confirmed the diagnosis. Partial thyroidectomy cured the "neurosis."

Anxiety is such a common symptom that one is frequently tempted, and generally justified, to make a diagnosis of hysteria. But here, too, the rule holds that if it sets in comparatively late in life one should make it with caution. Distinction is made between anxiety neurosis and anxiety hysteria. Both are accompanied by fears of death or insanity, of heart disease or cancer; but in the former the fears are more or less vague, whereas in the latter they are generally quite systematized and may amount to phobias or fears of being alone, riding in trains, etc. The neurotic anxiety is commonly attributed to direct sex frustration, such as, masturbation, coitus interruptus, forced

abstinence or *ejaculatio praecox*. The hysterical anxiety has a more complex psychic structure, frequently occurs apparently unmotivated, and may wake a patient out of sleep. Both are apt to occur in younger persons. The organic condition to be thought of is *angina pectoris* or coronary disease. Naturally these do not occur very often in young persons. The anxiety in heart disease is a rather normal reaction to a very genuine and serious threat. Blood pressure studies, electrocardiograms, the types of accompanying pain, and the whole setting generally serve to make the correct diagnosis. Hyperthyroidism may also be characterized by anxiety, but then there generally are very definite signs pointing to excessive function of the thyroid, such as sweating, *dermographia*, loss of weight, high basal metabolic rate. Difficulties are most likely to arise when an added neurosis masks a real organic condition. So-called "vasovagal crises" deserve passing mention.

While cerebral arteriosclerosis generally occurs past the age of fifty, it may set in much earlier and be characterized by such symptoms as fatigability, mood and other emotional changes, lack of power of concentration, slight lapses of memory, and disturbances in potency or libido—all of which may well pass for a *neurasthenia*. Careful examination, however, will reveal some hypertension, kidney involvement, cardiac enlargement, and peripheral sclerosis, especially of the retinal arteries. Occasionally these signs are lacking, but it is generally well not to make a diagnosis of cerebral arteriosclerosis unless at least some of them are present. To err in either direction and fail to bear in mind these very sound clinical teachings is frequently to court chagrin and sometimes tragedy. Not infrequently a patient is dismissed with the facile remark that there is nothing the matter with him only to learn that he later developed a cerebral thrombosis or hemorrhage or a progressive deterioration ending in dementia.

The early picture of Addison's disease, particularly the fatigue syndrome, may well appear as *neurasthenia*. Very soon, however, the low blood pressure, the diarrhea and the pigmentation of the skin and mucous membranes call attention to the real condition. In the beginning pernicious anemia may deceive the unwary. The loss of appetite, the vague pains, the tongue dysesthesias and other so-called "hypochondriacal"

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symptoms, particularly if they occur in women at the menopause age, may well be dismissed as neurotic. So may acroparesthesia with its peculiar sensations in the limbs and the slight vasomotor changes be confused with conversion hysteria.

The possibility of error, perhaps of the greatest import, lies in overlooking the early symptoms of general paresis which so often masks as a neurosis. Here slight memory lapses, imperceptible conduct disorders or undifferentiated moral deviations, lack of will power or ability to concentrate, perhaps a little euphoria or facetiousness alternating with depression and poor judgment, hypochondriacal preoccupation with bodily function, and a host of minor or otherwise insignificant complaints are apt to lead one astray. The fact that spontaneous remissions occur, further adds to the diagnostic difficulties and the possibility of error. Unless a careful history is taken and a meticulous examination made the patient may be told to "forget it," or take a vacation. The danger is all the greater because very early there may be no physical signs, such as pupillary anomalies, finger and perioral tremors, changes in reflexes, or impairment of articulatory speech, and only the positive serology of the blood and spinal fluid can make the diagnosis. In view of the fact that paresis has become a curable disease, oversight in diagnosis is of very grave import. It is worth remarking that occasional danger during the incipient or so-called "neurasthenic" phase of general paresis lies in the possibility that the patient may squander his fortune, offend against sexual and social morality or otherwise infringe on the law. This stage, so frequently overlooked, may very well become forensically important.

The last case cited illustrated the possibility of error in diagnosing hyperthyroidism as psychoneurosis, but in addition to the thyroid other glands of internal secretion may show dysfunction which is not easily recognized. The fact is that in both acute and chronic states of anxiety one may find symptoms simulating early hyperthyroidism, and incipient or advanced Graves' disease may be characterized by a variety of symptoms commonly attributed to the various neuroses. Anxiety, palpitation, tremor, digestive disturbances, occasional fatigue and diarrhea are common to both. Repeated examinations, therefore, and particularly study of the basal metabolic

rate, are as important as intensive psychiatric investigations. Hypothyroidism, too, not necessarily of the grade of myxedema, may be characterized by memory defect, apathy, depression, mental dulness, loss of interest and power of concentration, and digestive disturbances. Impotence may also occur, as it frequently does in hypo- or hyperpituitarism and in gonadal deficiency. I have seen at least 1 case of behavior disorder based on hypophyseal deficiency and cured by pituitary extract. How much ovarian or pituitary-ovarian dysfunction has to do with what passes for menopause neurosis is difficult to say. Certain it is that some correlation exists, even though its nature is not so well known. Occasionally gynergen does cure a menopause neurosis and at times follutein is beneficial. Much less is known of the relationship of the cessation of ovarian function to melancholia, but here too one may suspect, even though one cannot prove, that the two are not unrelated. The point is that endocrinopathies may pass for neuroses and neuroses may mask as endocrinopathies. The same may be said of dysfunction of the vegetative nervous system, though here the relationship is even less well understood. Some day we may learn of the relationship of the function of the hypothalamic region to the neuroses.

In young persons caries of the spine or tuberculous spondylitis may be mistaken for hysteria. It is easy enough to make the diagnosis if there is a gibbus or tenderness of the spinous processes, or if there are signs of compression of the spinal cord, and particularly if an x-ray is taken when bone changes are apt to be pathognomonic even early in the course of the disease. But very early none of these may be present, and the patient may well be dismissed as psychoneurotic. The danger is even greater in case of tumor of the spinal cord. For a long time there may exist only radicular pain, which is diagnosed either as an intercostal neuralgia or atypical sciatica or, worse still, labeled as hysterical. Even the experienced neurologist may err at a time when there are no reflexes changes, no impairment of motor power, no sensory disturbances at the level of the lesion or below it. Unless a spinal tap is done and changes in the spinal fluid are found or evidence of spinal subarachnoid block discovered, or x-ray of the vertebrae gives some clue to the existence of a tumor, it may not only be overlooked but not

even suspected. The diagnosis by exclusion in such cases, when no psychogenic factors are elicited, is particularly fallacious. Such errors are especially apt to occur in the case of latent carcinoma in older patients and of sarcoma in younger ones. The writer remembers particularly the chagrin he and his colleagues felt when after months of fruitless treatment, buffeting about of the patient as an incurable hysteric, and actual neglect, it was finally discovered that the young woman had a sarcoma of the spine which at first compressed roots and merely caused pain without any objective signs and only later compressed the spinal cord by invasion from without. The following case may be of some clinical interest.

A man, forty years of age, was referred for a neuropsychiatric examination because of pains and a host of psychoneurotic symptoms which he had had for years. Of late some of the pains had become more or less constant in the epigastric zone and others radiated to the urinary bladder region. There was something paroxysmal about the pains but otherwise they lacked special characteristics. Between treatments for a psychoneurosis, which he may have had, gastro-intestinal studies and investigations of the genito-urinary system were made, with negative results. The pains persisted and increased, but occasionally remitted as well, so that the diagnosis of psychoneurosis was maintained, all the more as the general findings thus far had been negative. Unfortunately there were no neurologic signs, and so the diagnosis was concurred in and no further effort made to study the case. A very grave error of omission, as it later turned out, was the failure to advise lumbar puncture. The patient finally did begin to show impairment of motor power in the legs, increase of deep reflexes, sensory disturbances, and urinary difficulties. This time a lumbar tap showed xanthochromic fluid, increased protein, and spinal subarachnoid block on manometric testing. Fortunately an extradural spinal cord tumor was removed and the patient recovered. Obviously, there is no reason why a psychoneurotic may not develop a cord tumor and none why one should permit the psychoneurotic symptoms to obscure an organic condition. It is of passing interest that many, though not all, of the neurotic symptoms vanished with the removal of the tumor.

Tumor of the brain, more particularly of the so-called "silent areas," may for a long time fail to give rise to violent headache, dizziness, vomiting, choked disk, or focal signs. Tumors of the frontal lobes may be characterized by symptoms which are commonly regarded as psychoneurotic. Some of them may be so exquisite as to simulate typical hysteria or obsessional neurosis, though they are more likely to appear as psychiatric manifestations of organic brain disease. I have

seen one instance in which the symptoms of a neurosis were so pronounced that the patient was psychoanalyzed for months. The error here consisted in the failure to look with suspicion on the persistence of a monosymptomatic neurosis and to re-examine the patient physically from time to time. There were extenuating circumstances, but the fact is that a quadrantic hemianopic field defect led both to the suspicion and the localization of a deep-seated temporal lobe glioma. Similar tragic errors have occurred before and are likely to occur again; in the case under discussion the error was softened by the fact that the tumor was irremovable from the very beginning. The rule may be laid down, however, that whenever there is the slightest suspicion of brain tumor encephalographic air studies should be made; the difficulty is that in cases when the diagnosis of psychoneurosis is made, tumor is not likely to be suspected. In such cases only repeated examinations can obviate errors.

In its early stage multiple sclerosis may possibly be confused with hysteria. Both occur in the comparatively young, remissions are common to both, and so are emotional disturbances, particularly euphoria and unmotivated laughter. However, definite organic signs characterize the first and their absence the second. Inequality of deep reflexes, absent abdominals, nystagmus, ataxia, a Babinski sign, speech disturbances, and pallor of the optic disks, are never seen in hysteria, whereas some or all of them characterize disseminated sclerosis. On the other hand, psychogenic factors are entirely lacking in the organic diseases and are written all over the hysterical symptomatology. Yet all of these criteria may fail one, as shown by a recent case which for ten or more years was treated for hysteria by several competent neurologists only to be ultimately recognized as a definite organic disease.

The subject of headache is altogether too vast to be dealt with in a brief discussion on differential diagnosis. Actually, because of the subjective nature of the symptom, there is no way of telling a hysterical headache from one based on organic disease, if for no other reason than the fact that the ultimate physiology of headaches is not well understood. Furthermore, it is difficult to tell, for instance, a so-called "toxic headache" or one following head trauma without accompanying objective signs of brain damage from a psychogenic one. Generally

speaking the psychogenic headache is more of a pain in the head or scalp, one frequently characterized by a variety of adjectives. Somehow the hysteric does not give the impression of true suffering, and occasionally a smile betrays the fact that the pain is not quite so unendurable as the meticulous description intends to convey. Migrainous or paroxysmal headaches, which are so frequently atypical, may well lead to diagnostic errors. Not all begin early in life, not all are periodic, limited to one side or followed by nausea or vomiting, a heredity history is not always present, and psychic factors may precipitate a migrainous attack. Both kinds are by far more common in women. The final diagnostic criterion, therefore, is the presence of definite psychogenic factors which account not only for the headache but for the numerous other hysterical symptoms which generally coexist.

While the diagnosis of hystero-epilepsy has been pretty generally discarded there are instances where it is difficult to tell between hysterical syncope and epileptic loss of consciousness. This much is true, however, that there never is loss of the pupillary light reflex in hysteria, there is not that absolute amnesia for the attack and there is not quite true coma. Rarely does the hysteric injure himself in falling, and true tongue biting, frothing, and incontinence also do not occur in hysteria. Postepileptic confusional states or epileptic furor may be mistaken for hysterical fugues, but here again there is absolute amnesia, one frequently elicits a history of convulsions, and the paroxysm is apt to be much briefer. The correct diagnosis is of extreme importance from a medicolegal point of view, as epileptics have been known to commit acts of violence up to murder during seizures characterized by furor. Finally, it is well to remember that the hysterical attack is practically always psychologically motivated; the epileptic one comes unheralded.

The question of so-called "hysterical tics" and spasms and chorea or other dyskinesias may be briefly dismissed with the statement that most of them are not hysterical at all. This is contrary to the old teaching, but if epidemic encephalitis taught anything it was to the effect that most of the dyskinesias can and do have an organic basis and that other organic signs may be entirely lacking. In any case hysterical chorea is a mis-

nomer; a movement is either choreic or hysterical. Tics are mostly organic, but if they are psychogenic they are more likely compulsive phenomena. Torticollis probably always is organic, and very likely a fragment of dystonia. Neither myoclonus nor athetosis is hysterical. It is a fact, though, that most of the dyskinesias, especially dystonia musculorum deformans, are at first diagnosed as hysterias.

In the case of occupational neuroses, it is well first to rule out such organic diseases as neuritis, tabes and syringomyelia or such symptoms as dystonia, astereognosis and apraxia. One should look very carefully for changes in reflexes, fibrillations, atrophies, sensory disturbances and responses to electrical testing. The nature of the occupation and the presence of psychogenic factors do not always decide, but they are of considerable help.

Finally, a word about hysterical pains sometimes known as "psychalgias." In a recent paper<sup>1</sup> on abdominal pain as the result of brain disease I showed that such pains do occur and that they are generally overlooked. It is a matter of common experience to see patients operated upon for "gastric ulcer, gallstones, appendicitis, etc.," which they never had. It is equally true that abdominal pain alone or associated with gastric or duodenal ulcer can occur on the basis of organic brain disease, especially tumors. While it is not known whether involvement of the cortex, the subthalamie region or the vagus center is responsible for the abdominal syndrome, the mediation of the impulses must be via those structures. The question, therefore, arises whether so-called "hysterical pains," especially abdominal, are not in effect the result of disturbed brain physiology and whether the dismissal of a patient with the cavalier statement that "he is a belly-acher" is not only bad psychology but poor physiology and worse medicine.

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### PRENATAL CARE

PRENATAL care is complete medical supervision of the pregnant woman. The aim is preventive rather than restorative, a purpose well within the scope of every conscientious practitioner.

Antepartum supervision unquestionably plays an important rôle in preserving the health of both mother and baby. The maternal mortality rate, the incidence of stillbirths and neonatal deaths are influenced by adequate care during pregnancy. Furthermore, we believe that a relationship could be shown between antepartum care and the quality and results of service at delivery. Admittedly lack of skill and judgment during labor may offset the good effects of such care. Then, too, an occasional bad outcome is probably inevitable as the result of obstetric accident or emergency. Nevertheless to bring the expectant mother to delivery in the best possible health, and for the attendant to be armed in advance with a knowledge of all possible complicating factors, would seem to be a valuable advantage.

Superficial and perfunctory care during pregnancy may, however, be worse than none at all, for as Munro Kerr points out both doctor and patient are given a false sense of security. Adequate supervision implies much more than casual advice about some minor disorder or an occasional examination of the blood pressure and urine. An early determination of the exact physical status of the patient is implied. Application of a knowledge of the nutritional aspects of pregnancy, the prevention of anemia, prompt detection and treatment of toxemia, the early diagnosis and control of syphilis, the discovery and correction of malposition, and an appraisal of the relation of

birth passage to passenger—all these are implied in adequate prenatal care. A broad application of the accepted standards of prenatal care requires a medically trained person; as DeLee has stressed, it means raising the plane of obstetric care.

The expectant mother should consult her physician as soon as a menstrual period has been skipped. A tentative diagnosis of pregnancy may usually be made on the basis of presumptive signs and symptoms. Biologic tests for pregnancy are seldom indicated since extra expense is incurred for information which a short lapse of time makes obvious. During the early, so-called "negative phase" of gestation more frequent visits to the doctor than is usually customary are of advantage, in enlisting the patient's interest and establishing confidence. Many minor ills are anticipated and prevented in the first few weeks.

By a thorough general history and physical examination intercurrent or associated conditions inimical to pregnancy are discovered. Inquiry is made concerning a past history of scarlet fever, diphtheria, pneumonia, rheumatic fever, recurrent attacks of tonsillitis, kidney disease and heart disease. The history of past surgical procedures are noted, especially operations involving the pelvic organs since certain types of suspension of the uterus or amputation of the cervix may produce difficult labor.

The patient's present status is recorded as regards appetite, sleep, bowels, urination and average weight. Concerning the menstrual history the physician wishes to know about the regularity, frequency, duration, amount and possible associated pain. From the date of the last menstrual period the probable date of confinement is estimated by adding seven days to the first day of the last period and counting back three months. The expectant mother should be firmly impressed with the fact that the exact date the baby is due cannot be estimated—that variations of two weeks either way may be expected and looked upon as normal. With a history of previous pregnancies, inquiry should be made as to the prenatal period, labor and puerperium, type of labor, mode of termination, size and condition of the baby. All possible information helpful in the present situation should be sought.

The following medical conditions are often complicated by pregnancy: (1) organic heart disease, (2) tuberculosis, (3)

chronic nephritis, (4) diabetes, (5) thyroid disturbance. Pregnancy found associated with the above should always be looked upon as the secondary or complicating condition. The problem of intercurrent conditions should be approached from the standpoint of internal medicine. Individualization is always necessary, with consideration of all factors, mental and environmental, in a given case. Here indeed the physician is reminded of the Hippocratic aphorism that experience is fallacious and judgment difficult.

While not within the scope of this paper to enter into the details of the management of these associated conditions in pregnancy, a brief comment about each in relation to prenatal care seems in order. Early discovery is in itself of the utmost value, enabling the physician to consider the advisability of interruption of pregnancy at the most opportune time or to institute appropriate treatment without delay. E. Allen and A. P. Bauer believe that future statistical studies of maternal and fetal deaths should include a critical analysis of the patient's health as a great factor in the obstetric end-results rather than basing conclusions entirely on the outcome of surgical obstetric procedures.

**Organic Heart Disease.**—Patients with organic heart disease belonging to Classes I and IIA generally do well during pregnancy. With a history of previous congestive failure or with failure early in pregnancy, the mother would seem to be running an unjustifiable risk. The treatment of decompensation is the same as in the nonpregnant. No attempt is made at surgical intervention during the acute attack. The cooperation of a cardiologist is essential.

**Tuberculosis.**—A wide diversity of views are found concerning all phases of the problem of tuberculosis complicated by pregnancy. General agreement exists that prior to the third month of pregnancy, a woman with active tuberculosis should be interrupted. If tuberculosis is discovered after the third month pregnancy should be allowed to continue. The value of collapse therapy when indicated and of sanatorium treatment are stressed by many authorities.

**Chronic Nephritis.**—Diagnosis is difficult and may be impossible during pregnancy. The condition is rare. Evidence of kidney damage must be sought for by repeated kidney func-

tion tests. Of these the renal concentration test, the phenol-sulfonphthalein test, and the urea clearance test are accepted as the most valuable. Blood chemistry examination for possible nitrogen retention and study of the eyegrounds for retinitis should be done. While the accepted treatment is interruption at any stage at which diagnosis is made, this is not always possible in the individual case.

**Diabetes.**—Since the insulin era there has been an increase in the number of diabetics bearing children. Glycosuria in pregnancy may be due to dextrose or lactose. True diabetes should be ruled out by blood sugar determinations and sugar tolerance tests. Control of the disease by proper diet and the careful use of insulin necessitates close supervision throughout pregnancy. The diabetic is prone to preeclampsia creating a grave problem. A knowledge of dietetics and of insulin therapy is required to protect the patient against acidosis, glycogen depletion and hypoglycemia. The usual diet should be given as regards providing mineral elements and vitamins. From 150 to 300 Gm. of carbohydrates should be taken. Control by urinalysis and blood sugar estimations should be carried out with increasing frequency in the last weeks of pregnancy. Frequent small doses of insulin are preferable to infrequent large doses.

**Thyroid Disease.**—Normally there occurs a physiologic increase in the basal metabolic rate reaching a maximum of 20 per cent in the last trimester. The work of Litzenberg and Cary indicates that with a low basal metabolism in early pregnancy, thyroid medication may prevent abortion. There seems to be a subjective improvement in patients with a low metabolic rate where small doses of thyroid are given in conjunction with hygienic measures.

Hyperthyroidism is a rare condition in pregnancy—interruption is not indicated. Mental rest, that is freedom from worry, fear and strain, as well as physical rest is important. Sedatives should be prescribed in conjunction with the administration of iodine in the form of Lugol's solution.

**Obstetric Examination.**—The unreliability of external measurements of the pelvis is generally conceded. Thoms among others having pointed out the inadequacy of external pelvimetry. However, with this in mind the interspinous and

the intercrystal measurements and the external conjugate should be recorded. An external conjugate below 18 cm. generally indicates contraction at the inlet; a normal external conjugate may be present, however, in a poor pelvis.

Vaginal examination is indicated at the first prenatal visit for the diagnosis of pregnancy, to determine the position of the uterus, the possible presence of fibroids or ovarian cysts or infection in the lower generative tract. Smears are taken from the urethra and cervix only as indicated.

No attempt is made to treat the retroverted pregnant uterus by manual replacement or pessary. The patient is instructed how to take the knee-chest position and advised to sleep on her abdomen.

Internal pelvimetry is of great value in estimating the capacity of the pelvis. If the promontory is felt, the diagonal conjugate is measured and 2 cm. subtracted to obtain the true conjugate. Note whether the sacrum curves well back. Palpate the spines and estimate the length of the sacrospinous ligaments. If well over 2 fingers the sacrosciatic notch is probably wide—a narrow notch indicates an android type of inlet. The slope of the side walls can be noted and the width and length of the pubic arch. Findings should be rechecked at the seventh month.

**Hygiene of Pregnancy.**—This includes consideration of the nutritional aspects of pregnancy, rest and exercise, bowel hygiene, care of the teeth—in fact, all aspects of the mother's way of living which influence health.

The influence of food on child-bearing has received increasing recognition. The dietary management of pregnancy requires precise instruction and the correction of current misconceptions. A well-balanced optimal diet rather than a merely adequate one is indicated.

The expectant mother should be impressed with the fact that the following basic daily diet is absolutely necessary:

- 1 quart of milk.
- Fresh and cooked fruit.
- 1 cooked green vegetable.
- 1 raw green vegetable.
- 1 egg.
- Lean meat including red meats, and liver once a week.
- Cereal.

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- Lean meat including red meats, and liver once a week.
- Cereal.

The caloric requirements of pregnancy are met by an intake of 2400 to 3000 calories. The above basic diet furnishes at least 1000 calories. The patient who is underweight at the beginning of pregnancy may require up to 4000 calories. The overweight patient should not reduce during pregnancy, but minimal gains are made on a 2000 caloric diet. No attempt is made to control the weight of the baby by diet since even were this possible it would be inadvisable because of the danger of depriving both mother and fetus of essential foodstuffs. The total weight gain during pregnancy should be 20 to 25 pounds. In the last trimester of pregnancy the gain should be limited to around 1 pound a week.

Formerly it was customary to restrict nitrogenous foods—indeed “no meat, no fish, no eggs” was a common slogan taught the expectant mother. The pregnant woman needs around 100 Gm. of protein daily. Meat, eggs and milk contain proteins of high biologic value, that is, containing the amino-acids essential for growth and maintenance. Strauss believes that restricted dietary intake of protein in pregnancy is harmful and that no injurious consequences follow administration of diets high in protein to women with toxemia of pregnancy.

The mineral requirements are best met by the intake of 1 quart of milk daily, assuring an intake of 1.2 Gm. of calcium and 0.9 Gm. of phosphorus. Vitamin D has a definite effect on calcium and phosphorus absorption, therefore if the patient is unable to take milk, dicalcium phosphate may be prescribed with viosterol. In addition to milk the use of fruits and green vegetables should assure an adequate supply of vitamins. A diet containing a sufficient amount of these so-called “protective foods” is the main essential. The protection of the mother’s bones and teeth, the avoidance of certain minor disorders such as subcutaneous edema, itching, paresthesias, and cramps in the calves of the legs, are dependent upon calcium and certain vitamins notably D. An adequate diet is also the best preventive of anemia during pregnancy. Iron, calcium and vitamin preparations are best prescribed only on indication.

In many of the handbooks for mothers the advice is given to drink 8 glasses of water daily. Arnold has pointed out the importance of controlling the fluid balance during pregnancy



in preventing severe toxemia. Patients with a past history of hypertensive vascular disease or with signs of incipient pre-eclampsia as evidenced by a slow, steady rise in the diastolic pressure should be taught to measure their fluid output and regulate the intake in accordance. One should not wait for frank edema to start balancing intake and output.

**Anemia.**—Determination of the presence of anemia is a part of prenatal care. At least one routine blood count and hemoglobin estimate at the seventh month would seem a wise procedure. Given an environment with insufficient diet, poor hygienic surroundings, lack of sunshine and outdoor exercise, and frequent acute infections, we may expect to find anemia of varying degree. Anemia in pregnancy falls into three groups. The so-called "physiologic hydremic anemia" is not a true anemia and should not be confused with simple nutritional anemias of mild degree which are common. The second group comprises the hypochromic microcytic anemia—a more severe form in which dietary deficiency plus disturbed gastric secretion are responsible. Reduced iron, 90 grains daily in small capsules, should be given in combination with liver therapy. The third type of anemia, the macrocytic, addisonian type, is very uncommon. Liver therapy supplemented by iron is used. In all severe anemias repeated small blood transfusions are of great value.

**Vomiting of Pregnancy.**—In the early weeks of gestation attempt should be made to prevent morning sickness and possibly the development of the severe form of hyperemesis by dietary means combined with psychotherapy. Six small meals a day should be eaten. Vitamin requirements should be met by plenty of the protective foodstuffs. Mineral waters and ginger ale are helpful. Hard candies supply much needed sugar. Constipation is corrected. If in spite of these measures vomiting persists, phenobarbital  $\frac{1}{2}$  grain, three times a day, is prescribed. Severe persistent vomiting demands more stringent treatment. Do not wait for dehydration, acetonuria and increased pulse rate before hospitalization.

**Dental Care.**—An early visit to the dentist in order that he may clear up possible foci of infection is necessary. There is apparently no greater tendency to dental caries during pregnancy than at any other time. Dental treatment and opera-

tions may be safely carried out at any time in the prenatal period.

**Antepartum Bleeding.**—Abortion is the chief cause of antepartum bleeding during the first two trimesters. The writer is skeptical as to the possibility of preventing spontaneous abortions by prenatal care because he believes that these are due in many cases to defects inherent in the ovum itself. The time to combat habitual abortion is preconceptional with attention to the health of both marital partners and the endocrine status of the woman. However, the use of progesterone in the early weeks of pregnancy is worth trying where abortion may be due to faulty implantation.

During the last trimester bleeding accompanied by pain points to premature separation of the placenta. Painless bleeding, no matter how trivial, should arouse suspicion of placenta praevia and requires that it should be ruled out. The patient should be placed in a hospital, her blood typed and a donor made available. In the interest of the baby internal examination should be deferred since manipulation may precipitate severe hemorrhage. If the presenting part seems deeply engaged placenta praevia may be ruled out although low implantation must still be considered. Where the presenting part is movable well above the symphysis the probabilities are that the placenta is implanted below it.  $\alpha$ -Ray will sometimes reveal the true situation.

**Syphilis.**—We wish to stress the importance of a routine Wassermann test early in pregnancy in private practice. Congenital syphilis is practically a preventable disease. The incidence of positive Wassermann reactions among private patients is probably less than 2 per cent. In a large percentage of prenatal patients with syphilis the disease is latent with no signs or symptoms helpful in diagnosis. While treatment should be started as early in pregnancy as possible still, as Speiser states, it is never too late in pregnancy to derive some benefit by treatment as far as the offspring is concerned.

**Toxemia.**—Early detection and treatment of preeclampsia is perhaps the chief reason for regular and frequent prenatal visits at which time the weight, blood pressure, and urinalysis are recorded. A sudden gain in weight due to water retention may be the first warning of toxemia. A rise in blood pressure

above 140 should immediately be heeded. To a certain extent the degree of hypertension is proportionate to the toxemia; this is also true as regards proteinuria. Prenatal care cannot be considered adequate where in the presence of rising blood pressure and increasing proteinuria prompt treatment is not instituted since in the majority of cases by conservative means the patient may be carried to or near term with a favorable outcome.

Hospitalization is usually required to secure adequate bed rest, and to study the possibility of renal impairment. Sedation with bromides, 15 grains, or phenobarbital,  $\frac{1}{2}$  grain three times a day, is useful. Record is kept of the urinary output and the intake of fluids restricted in the mild cases to two thirds the previous day's output. In the presence of marked edema no fluids are given for the first twenty-four hours. Sodium salts are restricted but proteins are given,  $\frac{2}{3}$  to 1 Gm. per kilo body weight. One hundred cc. of 50 per cent solution of glucose are given intravenously and repeated every four hours as indicated. Intravenous magnesium sulfate, 20 cc. of 10 per cent solution repeated as indicated, may also be given in the more severe cases.

If, after rest, sedation, dietary restriction, elimination, intravenous hypertonic glucose and magnesium sulfate, the patient's condition remains unimproved or becomes worse, the problem of interruption arises. A persistently high diastolic pressure is evidence of angiospasm. Examination of the eye-grounds for evidence of angiospastic lesions of the retinal arterioles is helpful. Note whether the reflexes are hyperactive. There is considerable evidence that to allow the severely toxic pregnant woman to go on is to allow permanent damage to her cardiovascular renal system. Induction with delivery from below is the method of choice in those cases, especially multiparae near term, with favorable soft parts. Otherwise, cesarean section performed under local anesthesia is the procedure of choice. Inhalation anesthesia should not be used with the possible exception of cyclopropane.

**Eclampsia.**—Every pregnant woman is a potential eclamptic. We aim to prevent the severely toxic patient from going on to the convulsive stage. This is not always possible even with adequate prenatal supervision since fulminating cases do

occur. Even here it is an open question whether with closer watch and better cooperation on the part of the patient the convulsive stage might not be reached. The patient with convulsions should be treated by conservative methods. Forcible delivery from below or cesarean sections are contraindicated because of the poor results. The patient should be in a dark room, kept quiet, morphine given and also intravenous glucose and magnesium sulfate. Gastric lavage, hot packs, and colonic irrigations are no longer used. When the disease has been controlled interruption may be considered.

**Disproportion and Malposition.**—Beginning with the fifth month the patient should be “tabled” for abdominal examination at each visit. Perhaps no procedure is of more value than inspection, palpation, auscultation and mensuration of the abdomen and every opportunity should be sought to become familiar with this simple technic. The height of the fundus is measured with a pelvimeter and recorded. The fundus reaches 29 cm. and then drops slightly at term, especially in primiparae. The McDonald measurement taken with a tape is another useful procedure. One end of the tape is placed at the upper border of the symphysis while the other is held by the thumb in the palm of the hand. The fingers or the upper hand are held at right angles to the fundus of the uterus, and the tape follows the contours of the uterus except at the upper border where the fingers make a tangent to the tape. After the sixth month this measurement divided by 3.5 gives the duration of pregnancy in lunar months—at term it is 35 cm. and the fetus is of average size. A measurement above 35 cm. suggests a large baby, hydramnios or twins.

Examination of the abdomen at each visit should reveal an abnormal position of the baby. Studdiford believes that with improvement in antepartum diagnosis and with routine use of external cephalic version in all suitable cases, the gross mortality of breech delivery would be reduced greatly. External version is contraindicated in multiple pregnancy and placenta praevia. The baby usually remains a vertex after turning which is performed on or after the seventh month. Repeated attempts should be made. The rather rare but dangerous transverse presentation may also be corrected but has a tendency to recur.

At the seventh month a careful internal examination is indicated to recheck the pelvis. The problem of disproportion looms in every labor—will the head come through? Failure to recognize the presence of grave pelvic deformity in a case which terminates fatally after a prolonged labor is a sad outcome which in some cases at least must be considered due to poor prenatal care.

As the abdominal examination is repeated each weekly visit in the last month, the physician looks for evidence of disproportion. A distorted pelvis is rare and easily recognized. The head may be deeply engaged or dipping well into the brim so that it is fixed. If the head is freely movable from side to side above the brim one should be on guard. The head may be high merely because of excessive fluid or unretracted lower uterine segment. Can the head be pushed into the inlet by gentle pressure on the fundus? Is there overriding and a pendulous abdomen? Where doubt exists as to the actual situation one should resort to x-ray and consultation.

**x-Ray.**—Roentgenography is a valuable aid in obstetric diagnosis. It will reveal the presence of twins, abnormalities of the fetus, such as anencephalus, and gives information as to position and presentation. It is being used in the diagnosis of placenta praevia.

Roentgen pelvimetry deserves wider use in prenatal work. There are various methods now in general use. An example of the frame (positions) method is the centimeter grid procedure of Thoms which gives a clear idea of the size and shape of the inlet. Study of the inlet by whatever method used should always be supplemented by a lateral view of the pelvis and by a view of the outlet. There is a tendency to consider disproportion as a problem of the inlet alone; it does not always follow that because the inlet is ample, serious difficulty will not be encountered at the lower levels. The lateral view is valuable in showing the relation of the presenting part to the birth passage. The true conjugate may be measured, the shape and position of the sacrum studied and the type of notch. All x-rays of the pelvis are more useful the nearer the patient is to term.

At Bellevue Hospital we have been particularly impressed with the advantages of the Caldwell and Moloy method of

stereoroentgenography for the study of the pelvic architecture. The method is useful even where the precision stereoscope is not available. By x-ray study of the pelvis elective cesarean section may be determined upon in advance in a small number of cases where absolute disproportion is found to exist. The majority of cases will be found to have ample pelvises but a knowledge of the shape of the pelvis has proved a valuable aid in the clinical conduct of the case. To obtain this knowledge antepartum is to bring one more factor influencing the outcome into the realm of certainty. The size of the baby as a factor in disproportion also needs consideration. Exact cephalometry is not required. Either the lateral view or stereoscopic plates taken near term give a clear idea of the relation of the fetal head to the birth canal. The physician may now await the onset of labor with equanimity although at least two unknown factors still remain—the possibility of prolapsed cord and the possibility of functional or soft part dystocia. Finally the question of induction of labor arises during the course of prenatal supervision. No matter how simple the method used, induction carries with it special risks. Therefore, the indications should be clean cut and urgent. Never should it be done as a mere matter of convenience or because of importunity. Induction has never found favor in this country as a method of treatment for contracted pelvises.

Where home delivery is contemplated the patient should be advised concerning the necessary supplies and preparations. All patients should be instructed as to the signs of beginning labor and advised to report immediately the onset of any pains, or the passage of fluid or blood.

In conclusion, we believe:

1. That prenatal care implies constant and efficient supervision with hospitalization for those conditions too serious to be adequately coped with at home.
2. That the diagnosis and management of intercurrent or associated conditions complicated by pregnancy necessitate individualization and the aid of internal medicine.
3. That the nutritional aspects of pregnancy deserve consideration in the prevention of deficiency states.
4. That congenital syphilis is a preventable disease.
5. That effort should be made to prevent eclampsia by

prompt attention to signs of hypertensive vascular disease evidenced by a progressive rise of the diastolic blood pressure, proteinuria, upset water balance and spastic changes in the retinal arterioles.

6. That antepartum bleeding necessitates ruling out placenta praevia.

7. That malposition, especially breech, should be corrected where possible.

8. That the relative size of the birth canal and passenger should be determined in advance for possible disproportion and that roentgenography should be utilized.

9. That the physician who realizes he has two lives confided to his care will approach the privilege of prenatal supervision of expectant mothers as the biggest job in preventive medicine he now has to do.

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DANGERS OF DEHYDRATION TREATMENT IN  
HEART DISEASE

IN this paper the authors propose to consider certain untoward effects of diuresis and dehydration therapy with suggestions for their prevention and treatment. Because of their remarkable efficiency, mercurial diuretics will receive special consideration although this discussion would pertain with equal force to other potent diuretic agents.

It has long been realized that elimination of excess fluid from the body tissues is in itself a distinct aid to cardiovascular efficiency, producing both subjective and objective improvement. The mechanism of this change has been the subject of considerable investigation. It may be due in part to a diminution in peripheral resistance and to a transient decrease in blood volume, which has been definitely shown to occur.<sup>24</sup> Friedman and his associates<sup>1</sup> attribute the improvement to: (1) a decrease in the load of the heart; effected by producing a decrease in the flow of blood through edematous tissues in proportion to the metabolism, the resulting decline in venous return and in venous pressure tending to decrease the cardiac output; (2) an increase in the ability of the heart to carry the load by reducing myocardial edema and thus increasing the contractile power of the heart.

Not infrequently the diuretic effect of the xanthines and even of the "sheet-anchor" of cardiac failure—digitalis—is disappointing. In 1920, a new and potent diuretic drug was added to the therapeutic armamentarium. Saxl and Heilig<sup>2</sup>, employing novasurol (merbaphen), an organic mercurial com-

pound, in the treatment of luetic aortic disease found that drug produced remarkable diuresis in decompensated cases. When, in 1924, Keith and his associates<sup>4</sup> reported the utility of calcium chloride in diuretic therapy of nephritis the study of dehydration received another impetus.

The new mercurial compound, novasurol (merbaphen), was widely hailed and extensively utilized. A series of related drugs—salyrgan (mersalyl), novurit, neptal, mercupurin—was rapidly developed and used with satisfaction. These drugs are so superior to any of their predecessors that any discussion of untoward effects of dehydration must involve a discussion of their action, although, as already indicated, any effective diuretic could produce similar results.

As experience accumulated, certain undesirable effects of the mercurial compounds were observed. These may be classified as follows:

1. Fatality shortly after the administration of the drug.
2. Local tissue necrosis, phlebitis, neuritis.
3. Symptoms of mercurialism.
4. Purpura.
5. The syndrome of restlessness, mental confusion, apathy, coma, and—in some instances—death.
6. Combinations of 3 and 5 as occurred in one of our cases.

Rapid fatality<sup>5, 6, 7</sup> is interpreted as idiosyncratic<sup>6</sup> anaphylactoid, as a "speed shock" phenomenon<sup>8</sup> or possibly as due to cardiovascular collapse as seen in adrenalin poisoning (see the Discussion of Jackson's work<sup>9</sup> on the pharmacology of the mercurial diuretics). The best safeguard against this type of accident is slow injection when the intravenous route is used. Local tissue damage is avoided by accurate placement of the drug in vein or muscle when these routes are used. Symptoms of mercurialism occur very occasionally.<sup>10, 11, 12</sup> Since the use of the mercurial diuretics is usually characterized by a "thrust excretion" the drugs are rapidly eliminated except when they fail to act efficiently. In other words, the danger of mercurialism probably varies inversely with the degree of diuresis and the two are to a certain extent mutually exclusive. Nevertheless, it should be remarked that when the first injection is unsuccessful a second may safely be administered after forty-eight hours. Symptoms of mercurialism have been reported

with salyrgan by Rosenthal,<sup>11</sup> necropsy revealing colitis, tubular nephritis and, in addition, pulmonary embolization. Similar findings were recorded by Snell and Rowntree<sup>12</sup> in their paper on purpura following the use of mercurial diuretics. The syndrome of restlessness, mental confusion, apathy, and coma is the most serious complication of dehydration therapy and is the one with which this paper is concerned. It has been previously described by the authors<sup>13</sup> and other writers.<sup>14, 15, 16</sup>

It is important to reiterate that no indictment of the mercurial diuretics is intended. These drugs are indispensable in the treatment of many varieties of water retention and their value cannot be overestimated. However, we propose to outline certain methods by which they may be used with even greater safety than heretofore. To do this, it will be necessary to consider briefly the pathologic physiology of dehydration in general, the pharmacology of certain diuretics and especially of the mercurials, the contraindications to severe dehydration therapy, the syndrome of excessive dehydration, the antidotal measures to be employed if dangerous symptoms supervene.

#### PATHOLOGIC PHYSIOLOGY OF DEHYDRATION

Examples of untoward effects of dehydration are found in a wide variety of pathologic states in which salts and water are lost from the body. The algid form of cholera<sup>17</sup> and the alimentary intoxication of infants are examples. The prime importance of water and salt depletion in the latter condition has been clearly demonstrated by the admirable work of Karelitz and Schick<sup>18</sup> who have shown that the restoration of water and salts (together with transfusion) is often life saving. It is obvious then that untoward effects of dehydration may be observed in cases in which no diuretic therapy is used.

While a number of different ions are present in the body cells and fluids, it is well established that sodium is the most important for holding water in the intercellular tissue spaces<sup>19</sup> and that it plays an extremely important rôle in the hydrodynamics of the body. With loss or gain of fluid there is a corresponding loss or gain of sodium. Consequently, although the other ions may be of some importance in water metabolism it is sodium and water particularly which have a particular bearing on the syndrome emphasized in the present article.

## PHARMACOLOGY OF DIURESIS AND DIURETICS IN GENERAL

Diuresis in general<sup>20</sup> is characterized by loss of water and of cations in the proportion in which they occur in blood plasma and extracellular fluids; *i. e.*, 145 milliequivalents of sodium, 4 milliequivalents of potassium and 4 milliequivalents of calcium per liter. Chloride is excreted in larger amounts than the basic ions, *i. e.*, 190 milliequivalents. The greater the diuresis, the longer is the time required by the body to regain its fluid. The larger the subject, *i. e.*, the greater the available amount of body fluid, the greater is the diuretic response. In this connection it is important to remember that the presence of edema is no assurance that the patient is not suffering from a lack of *available* salt and water. He may complain of great thirst and present poor turgor of the tissues of the upper half of the body. To overcome the emaciation associated with diuresis in experimental animals used for determining minimal toxic doses of mercurials it has been found that fluid administered by mouth is more effective than that given parenterally.<sup>21</sup>

## SPECIAL PHARMACOLOGY OF THE MERCURIAL DIURETICS

The mode of action or pharmacology of salyrgan remains a matter of debate. The theories may be briefly summed up as follows:

1. The hydrophilic properties of the tissues are diminished.
2. An adrenalin-like action of prolonged duration is produced.
3. An inhibiting effect on the renal tubular epithelium is developed.

The first theory is based on the antidotal effects of supplying fluid to the body and of giving posterior pituitary extract; in other words, it suggests an alteration in water metabolism and postulates an initial blood dilution which is not borne out in fact.<sup>22, 23, 24, 25</sup> Schmitz<sup>24</sup> made determinations of the refractive index of the blood plasma every three minutes after the administration of salyrgan and found no hydremia; on the contrary, the refractive index increased during diuresis indicating hemoconcentration. The early reports of initial blood dilution (increase of hydremia) are now attributed to overemphasis of minor variations and to the time intervals at which determinations were made. Nevertheless, that water metab-

olism is faulty in these cases cannot be denied, since, as already pointed out above, it is well known that a patient may be edematous in the lower extremities and complain of severe thirst and present poor tissue turgor over the upper half of the body. The second theory is based on the interesting studies of Jackson<sup>9</sup> which show that salyrgan is analogous to adrenalin in its action upon the heart, blood vessels, and kidney. The third theory, namely, that the activity of the renal tubular epithelium is depressed, preventing resorption of threshold substances, notably sodium chloride and water is the most generally accepted at the present time. Nonnenbruch,<sup>23</sup> like Schmitz, has shown an initial decrease in hydremia. Chabanier, Lebert, and Lumière<sup>22</sup> have shown an initial drop of blood sodium—in one instance from 5.83 to 2.48 Gm. per liter—and of blood chloride from 6.38 to 3.52 Gm. per liter. For further interesting data in this connection Govaert's studies<sup>26</sup> with transplanted kidneys may be consulted.

Fourneau and Melville<sup>21</sup> in studying toxicity of mercurials made the following important observations. Too rapid injections may cause instant death in a rabbit which would otherwise survive seven to fourteen days. This corresponds precisely with fatality shortly after the administration of the drugs as noted in the earlier part of this paper. Acute intoxication may occur and cause emaciation and death in five days; it is characterized by anuria, diarrhea, and renal and intestinal lesions. Chronic intoxication is associated with some degree of diuresis, terminal diarrhea and renal changes. The authors state that the minimal toxic dose is that weight of the substance expressed in Gm. per kilogram of rabbit which when injected intravenously into animals kept on a *basal water-free diet* leads to *progressive emaciation and death* in seven to fourteen days. This syndrome is distinctly analogous to the one which we describe in human subjects. The mechanism of this chronic intoxication is attributed to *some derangement in water metabolism* (which we would modify to *water and salt depletion*) rather than to an associated nephritis. These authors have made the extremely important observation that when their animals were given water by mouth (200 cc. into the stomach) diuresis would ensue and the animals would recover. They confirmed the observation of H. Gunsberg<sup>27</sup> that water by

mouth is more effective than water administered parenterally. These observations of Fournau and Melville and of Gunsberg form the basis for our method of managing cases of excessive dehydration.

It has been shown that in diuresis due to salyrgan and its allies there is a huge excretion of sodium chloride and water.<sup>20</sup>

It is important to understand that the degree of diuresis is dependent upon the amount of mercurial administered. When the dose of merbaphen is increased from 1 to 2 cc. there is a threefold increase in the excretion of water and sodium chloride and a twofold increase in the duration of the action.<sup>20</sup> The various drugs are available commercially in approximately 10 per cent solutions and it is advisable to begin with a small dose ( $\frac{1}{2}$  to 1 cc.) intramuscularly.

The most popular route for the administration of the mercurials is the intramuscular. Although a number of the drugs may be safely administered intravenously, there is in many instances no distinct advantage to this route. Recently it has been found that rectal administration in the form of suppositories is often effective.

#### CONTRAINDICATIONS TO THE USE OF THE MERCURIAL DIURETICS

In an effort to explain the pathogenesis of the various toxic phenomena of the dehydration syndrome and to determine contraindications, our cases and those reported in the literature have been examined from the standpoint of age, sex, height and weight, type of disease, blood pressure, renal function, degree of diuresis, state of dehydration, urinary changes, blood chemical findings, mode of exitus, postmortem findings, drug employed, and dosage. Sprague and Graybiel<sup>15</sup> found that age, sex, blood pressure, duration of disease, degree of cardiac enlargement, and cardiac rhythm were unimportant in predicting the efficacy of diuresis. Usually the reports of various authors are incomplete and a tabular analysis cannot be made. Nevertheless it is our impression that elderly, atherosclerotic individuals may be less able than others to effect an automatic readjustment of salt and fluid balance after diuresis, particularly if they are thin or cachectic (*i. e.*, with a small available amount of salt and fluid to provide them with a margin of

safety), if already in a poor state of hydration, and if the dosage of the drug has been large.

### THE SYNDROME AND ITS DIFFERENTIAL DIAGNOSIS

The syndrome which we will now discuss in detail occurs with diuresis and is characterized by preliminary restlessness and mental confusion, delirium or even a psychotic state, followed in some instances by apathy, coma, and death. Extreme thirst with exceedingly dry tongue and loss of tissue turgor are often observed. The premonitory restlessness may not appear and apathy may be the first manifestation.

In this connection, it is interesting to observe that severe weakness without other symptoms is often noted after diuresis. This weakness actually represents the first phase of a complete syndrome; it is fairly common and is not dangerous. In patients under long-continued therapy for myocardial insufficiency this symptom is sometimes relieved by interrupting the usual routine for a period of one to two days during which liberal amounts of water and salt are permitted.

Any or all of the symptoms we have noted may occur concomitantly with complications inherent in the underlying disease process or in association with other superimposed complications. However, they are often distinguishable even in the face of these confusing factors and should always be borne in mind when a patient who has been subjected to diuretic therapy appears to be going downhill.

In other words when a waterlogged patient under the influence of diuretics begins to fail one must endeavor to decide whether any of the following conditions are present, and if so whether they are etiologic, contributory or only incidental to the clinical picture:

1. Irremediable myocardial insufficiency.
2. A fresh coronary thrombosis.
3. Exacerbation of acute rheumatic carditis.
4. Pulmonary infarction.
5. Respiratory tract infection.
6. Cerebral vascular accident.
7. True renal insufficiency.
8. Oversedation.

9. Acidotic coma from the use of acidifying salts in cases with impaired renal function.<sup>28</sup>
10. The syndrome herein described.

On close analysis it should be possible to distinguish the true nature of the patient's collapse, if it is borne in mind that he is undergoing diuretic therapy, and that this alone may be the causative factor.

#### MECHANISM OF THE SYNDROME

As has already been implied the syndrome which we describe is dependent on a disturbance in the water and mineral equilibrium of the body. As already stated in the section on pharmacology, Nonnenbruch and Schmitz have shown an initial diminution in hydremia and Chabanier *et al.* have shown an initial drop in blood sodium and chloride. Keith, Barrier and Whelan<sup>29</sup> have found that diuresis, either spontaneous or due to ammonium chloride and novasurol, is associated with an increased excretion of water *and sodium*; there is some loss of other ions but of none so constantly as sodium. This immediately calls to mind the acute collapse of Addison's disease which presents a clinical picture in many ways strikingly similar to the one which we describe—*i. e.*, profound weakness, apathy, coma—and in which the blood sodium is also depleted (Loeb, Atchley, and Stahl<sup>30</sup>) and which may be precipitated by deprivation of sodium. Loeb and his associates have found that the blood sodium (and blood sugar) fall while the blood urea rises and the other chemical and morphologic studies of the blood show evidence of blood concentration.

As pointed out in a previous paper<sup>13</sup> the description of this syndrome is not original with us. In 1898 Eichhorst<sup>14</sup> was able with digitalis and diuretin to produce marked diuresis after which somnolence, disorientation, delirium, and apathy developed in certain cases. Sprague and Graybiel,<sup>15</sup> in 1931, reported a case of malignancy with ascites in which it seemed that death was hastened by the use of salyrgan. A similar observation was made by one of us (Poll) in a patient with a carcinoma of the ovary, carcinomatosis peritonei, and marked ascites. The patient, an elderly woman, was otherwise in good condition. Two cc. of salyrgan were administered intramuscularly. Within twelve hours—after a marked diuresis—the



patient became very restless, quickly lapsed into apathy, followed by coma and death. Srnetz<sup>10</sup> in 1934 stressed the necessity for care in administering salyrgan in severe cardiac insufficiency and mentioned somnolence and mental confusion (phantazieren) following diuresis, but did not mention either the severity of the diuresis or the mechanism of the effects.

### PROPHYLACTIC METHODS AND GENERAL PLAN OF MANAGEMENT

As already indicated, a study of our case reports and those of other observers provides no entirely adequate basis for the prediction and exclusion of patients unfavorable for drastic dehydration therapy. Particular care should be used in the presence of senility, advanced atherosclerosis and cachexia. The renal function as determined by the concentrating power of the kidneys is important.<sup>10</sup> The initial dose should be small since the diuretic response is a function of the dose. If the preliminary dose is ineffective and a large collection of fluid is evacuated from a serous cavity the second dose of the diuretic drug should not be increased since under these circumstances an undesirably large diuretic response is sometimes evoked. It is important to proceed slowly with dehydration and to avoid carrying out too many procedures (such as phlebotomy, thoracentesis, paracentesis abdominis) at one time. This precaution applies particularly in elderly patients with predominating right heart failure.

At times it may be preferable to ignore mild asymptomatic grades of edema rather than to risk producing serious dehydration effects.

### ANTIDOTAL TREATMENT

The foregoing analysis gives the key to therapy in cases in which untoward symptoms have developed. The following measures are employed:

1. Oral administration of water.
2. Oral administration of sodium chloride at first in capsules and later as a 0.1 per cent solution which is effective in the restoration of the sodium content of the blood.<sup>81</sup>
3. Intravenous and subcutaneous administration of salt solutions if the foregoing methods are impossible. If therapy

is delayed the condition may no longer be reversible and may end fatally.

### REPORT OF CASES

The following cases form part of a group previously reported by the authors.<sup>13</sup>

**Case I.**—A sixty-seven-year-old white man entered the hospital with a diagnosis of generalized arteriosclerosis, including cerebral and coronary involvement, and myocardial insufficiency. He had observed exertional precordial pain for ten years and dyspnea and edema for four months. With sedatives and dehydration therapy including the restriction of salt and fluid and 2 intramuscular injections of mercupurin (1 and 2 cc. respectively), the patient lost 30 pounds. Thirteen days after his admission to the hospital and one day after the second injection of mercupurin, it was observed that the patient was suffering from profound weakness. On the following day mental symptoms developed and he became noisy and attempted to strike the nurses. It became necessary to transfer him to another institution.

This case is an instance of weakness and psychosis diagnosed at the time as "psychosis with cardiac disease" following diuresis.

**Case II.**—A sixty-five-year-old man entered the hospital for treatment of myocardial insufficiency due to disease of the coronary arteries. He was placed on dehydration therapy including 1 cc. of salyrgan administered intravenously. Although his original weight was only 94 pounds, he experienced a marked diuresis. The next day he became noisy and had delusions of persecution. It was necessary to administer morphine and chloral. Progressive weakness and obvious dehydration ensued. Despite the fact that fluids were then forced he became stuporous and died with a terminal temperature of 101.4° F.

This case illustrates the point that a patient with a small body weight, *i. e.*, with a small reserve of salt and fluid, should be dehydrated cautiously.

**Case III.**—A sixty-five-year-old woman was admitted to the hospital complaining of dyspnea and edema. The diagnosis was generalized arteriosclerosis, including coronary arteriosclerosis, myocardial insufficiency, right hydrothorax, and peripheral edema. On a dehydration régime including 3 injections of mercupurin, each of 2 cc., she lost 38 pounds in weight over a period of twelve days. At this point, when signs of decompensation had disappeared, and the patient was ready to be out of bed, she became drowsy and uncooperative. When fluids were then forced for a few days the symptoms cleared up, and the patient was able to leave the hospital much improved one month after her admission. Precisely the same sequence of events had been observed on 2 previous admissions to the hospital.

This case is one in which drowsiness and mild mental symptoms regularly followed the period of dehydration.

Case IV.—A sixty-five-year-old man entered the hospital complaining of dyspnea and orthopnea of four months' duration. The diagnosis was generalized arteriosclerosis, coronary arteriosclerosis, auricular fibrillation, chronic bronchitis and emphysema, and myocardial insufficiency. The patient received 3 injections, each of 2 cc., of salyrgan, one day, one week, and two weeks, respectively, after admission to the hospital. During the first two weeks he lost 30 pounds in weight and complained of severe weakness and diarrhea. Four days later stomatitis and pharyngitis developed and there was a slight rise of temperature. The patient became unresponsive and uncooperative, refusing food and fluids. His symptoms were at first ascribed to the use of chloral hydrate. Nevertheless fluids were forced for three days during which time the stomatitis and diarrhea subsided and the patient became more responsive and cooperative. He was permitted to gain several pounds without developing symptoms of congestive failure, and left the hospital one month after admission in good condition.

This is an instance of severe weakness and mild mental symptoms following severe diuresis. The symptoms of diarrhea and stomatitis were probably due to mercurialism although this feature of the case was not investigated. It is important to note that, although the unfavorable symptoms were at first ascribed to the use of sedatives, with the administration of fluids in liberal amounts recovery ensued.

Case V.—A fifty-seven-year-old woman was admitted to the hospital complaining of dyspnea and orthopnea and swelling of the lower extremities. The diagnosis was generalized arteriosclerosis, with coronary involvement, hypertension, and myocardial insufficiency with advanced peripheral edema. On dehydration therapy, including the use of ammonium chloride and neptal, she lost 32 pounds. As the congestive phenomena improved, mental confusion and restlessness appeared. Although there were no focal neurologic signs and no mental symptoms prior to dehydration, the symptoms were ascribed to cerebral arteriosclerosis plus cardiac decompensation. Despite the fact that no further injections of neptal were administered the general dehydration measures were not discontinued. Nevertheless the patient recovered.

After fifteen months the patient returned to the hospital with symptoms of increasing decompensation of five weeks' duration. Over a period of eighteen days, 3 doses of mercupurin were given with marked diuresis. The patient then complained of profound weakness and became uncooperative. On the eighteenth day symptoms of severe vasomotor collapse developed, the clinical picture resembling that of acute coronary thrombosis, though without electrocardiographic changes as compared to previous records. During the next three days fluids were forced and the patient's condition improved remarkably. She was discharged from the hospital after one month.

In this case the periods of dehydration were characterized by restlessness, mental symptoms, profound weakness, and a period of vasomotor collapse. By simply omitting further injections of neptal during her first stay in the hospital and by forcing fluids during her second stay, recovery followed.

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#### EPILEPSY: BIODYNAMICS AND TREATMENT

**Definition.**—Epilepsy is a disorder of the cerebral neurons characterized clinically by a tendency to recurrent fits. The fits are known now to be disturbances in the continuous electrical activity which maintains consciousness. Epilepsy is to be diagnosed, not upon any characteristic of the fits, which are of great variety, but upon this tendency to periodic recurrence.

**General Conception.**—A tendency to fits once definitely manifested, persists throughout life even from infancy to advanced age, although it may be submerged by medical treatment or improvement in general health. So fixed and constant a physical characteristic seems to justify the assumption of a basis in anatomic structure. But such an assumption is by no means unanimous. There has been no agreement upon any pathognomonic structural imperfection or defect as the basis for the tendency. In 1926<sup>1</sup> I adduced certain evidence to show that the varied pathologic anatomy of epilepsy has a common denominator which satisfactorily explains the fixed tendency. This common denominator is a paucity of functionally active, or impulse-carrying fibers. On the basis of the *developmental* or *acquired* origin of this pathology an etiologic classification can be made of *primary* defect and *secondary* defect epilepsy. As for primary defect epilepsy, the imperfections in development which have been noted in epileptic persons are many and varied, but a paucity of fibers is a consequence which can be ascribed readily to any of them. In secondary defect epilepsy, the functionally active fibers are reduced by changes accompanying destructive lesions, inflammatory, neoplastic, degenerative or traumatic, of the cerebral tissue, its coverings, or its

vascular and spinal fluid channels. Since that time pathologic studies and experimental work on epilepsy (particularly the electrophysiologic studies) have served greatly to increase the plausibility of my hypothesis.

The intermittent disturbances in physiologic function which are the fits have to do first and foremost with the skilled environmental contacts, that is, those processes which maintain consciousness. These physiologic disturbances can be explained in accordance with the specific anatomic fault of defective fiber (conduction) pathways, because consciousness with its expansion and contraction depends upon the transference of impulses among high cerebral units, in particular the receptive centers for sensory stimuli. This intercommunication is maintained electrically and the pathways for these communications are the nerve fibers. Over their network the transference of nerve impulses occurs which permits awareness of self and surroundings and the intellectual functions of attention, memory, deliberation and choice. So, after reviewing briefly the pathologic anatomy, I shall give my hypothesis of the pathologic physiology and illustrate it by describing the probable intracerebral occurrences during a single attack.

**Pathologic Anatomy.**—*Facts Proving It a Cerebral Disease.*—That the epileptic tendency is, first of all, a disorder of the cerebrum seems almost a superfluous statement in view of the fact that the essential feature of the fit is a disturbance of consciousness which is a function of the cerebrum. However, it has been established well by the facts of cerebral disease, electrical experimentation, ablation of certain portions of the brain, experimentation with convulsant drugs, and by a combination of these various methods of investigation, that epilepsy is a disease of the cerebrum and no place else. The same facts have shown the importance of the cortex in the clonic and the subcortical regions in the tonic features of the muscular spasms accompanying convulsions.

*Facts Proving Basis in Anatomic Structure.*—Apart from a life-long constancy of a once established tendency to fits various other facts argue for its basis in imperfect cerebral anatomic structure, such as the following: its close association with mental deficiency and its increased frequency with increased grade of mental deficiency; its greater liability at the



time of incomplete development of the brain in infancy; its common occurrence with destructive cerebral lesions of almost any kind or location; the fixity of the point of onset to a single location for any individual epileptic; the structural cerebral imperfections suggested by the frequent presence of gross bodily anatomic malformations.

*The Common Denominator in Pathologic Anatomy.*—The common denominator in such a varied pathologic anatomy can only be found in structure subserving a function common to all parts or identical in any cerebral location. The *pathways* which carry the intercommunicating impulses, alone fulfil the requirement. A lesion any place which destroys fibers will always produce one identical effect: a difficulty in transmitting the impulses to correlate the various cerebral functional units. That the common denominator of the pathologic anatomy of epilepsy, or the essential epileptic fault, is a paucity of functionally active correlating neurons, thus seems evident.

*Facts Substantiating Common Denominator Hypothesis.*—The close relationship of infancy to epileptic susceptibility is considered due to correlating neurons being incompletely awakened to functional activity by the delayed deposit of the myelin sheath. Three facts in the pathologic anatomy of epilepsy supply supplemental proof of culpability of correlating neurons in this basic instability.

Firstly, lesions chiefly in white matter, such as occur in so-called "demyelinating diseases," seem prone to set up the convulsive tendency. In Schilder's disease, encephalitis, periaxialis diffusa, the expression of which is destruction of myelin sheaths, fits may be the first symptom to draw attention to the patient's illness, but usually appear at some times during the course of the disease. In status dysmyelinatus described by the Vogts, convulsions are part of the clinical picture. King and Meehan<sup>2</sup> in their recent account of Marchiafava's disease, characterized by demyelination of nerve fibers in the corpus callosum, put epileptiform convulsions as the most constant somatic symptom. They quote Bignami and Nazari as obtaining a history of convulsions in 21 of the 22 patients who could give information on this point.

Secondly, the brunt of the disturbance in chronic epilepsy is borne by subcortical structure according to Hodskins and

Yakovlev<sup>3</sup> in their study of the nature and location of the pathology underlying the neurosomatic deterioration of chronic epileptic patients. Peculiar disappearance of fibers in the globus pallidus and corpus striatum, especially a loss of myelin sheaths, was recently demonstrated by Spiller<sup>4</sup> in a case of subcortical epilepsy. As the striate system has no direct cortical communications, but reaches the prefrontal and precentral convolutions by several series of neurons, the tonic convulsions described, and the irritability, loss of temper, tendency to stutter, difficulty in understanding what was read, and impairment of memory, were considered due to loss of function in these correlating neurons.

Thirdly, epileptic attacks occur most frequently in cases of diffuse, slowly infiltrating glioma in which many ganglion cells and nerve cells remain fairly intact between the growing tumor cells, according to List.<sup>5</sup> This type of tumor reduces fibers in number sufficiently to interfere with the facilitation of impulses but does not cause a complete paralysis of function as do the rapidly growing and thoroughly destructive tumors.

*Special Vulnerability of Frontal Lobe.—Autopsies Prove It.*—Autopsies on epileptics indicate the special vulnerability of the frontal lobe to the epileptic tendency, either through its lack of good structural development, or upon its invasion by destructive lesions. Bateman<sup>6</sup> recently reviewed the clinical and pathologic data in a series of 178 brains of persons with convulsions. Only 2 of the brains did not show pathologic change. He concluded that cerebral frontal agenesis was the most predominant and characteristic condition in the brains of patients whose symptoms occurred before the period of pubescence. He divided his material into three groups. One group of 34 included persons of all ages who had active organic disease of the brain. The rest were divided into two groups according to time of onset of convulsions before or after an arbitrary age of puberty as twelve. In the older group of 76 cases the most common pathologic changes were in the cerebrospinal fluid and vascular systems. There were structural developmental defects, but the majority were the result of inflammatory insults to the cerebrospinal circulatory system. In the younger group, whose convulsions occurred before the age of twelve, there were 66 cases and in all these there was

cerebral agenesis which in each instance included the frontal lobes.

*Tumor Statistics Prove It.*—Regarding the location in the cerebrum of tumors most likely to evoke epilepsy, statistics agree on the frontal and are approximately in accord in stating that convulsions occur in about 50 per cent of frontal lobe tumors. In Parker's<sup>7</sup> series, which may be considered representative of other statistics, convulsions occurred in 52 per cent of frontal lobe tumors, in 31.8 per cent of temporal lobe tumors, in 38.3 per cent of corpus callosum tumors, and 30.7 per cent of third ventricle tumors. When the tumor involved a combination of two such important association centers as frontal and temporal, convulsions occurred in every case.

*Pathologic Physiology.—Frontal Lobe Physiology.*—This special vulnerability of the frontal convolutions cannot be ignored in any consideration of the dynamics of epilepsy. But it must be remembered that all parts of the brain are connected with the frontal lobes, and that nervous function is "localized" in all those nervous structures which are thrown into activity in the performance of function. It is doubtful if any nervous activities occur in the cortex exclusively without some participation or reverberation on lower levels. Recent opinion regarding the preponderant physiologic function of the frontal lobe is practically unanimous in ascribing to it synthesis of impulses from all parts of the nervous system which are necessary to form a decision as to action concerning environmental contacts.

Any intrinsic disturbance of the frontal lobes which causes a difficulty in the synthesis of impulses arriving there, leads to a state of indecision and mental confusion. Disturbances in other areas of the brain important for the reception and association of sensory impulses or in pathways relaying such impulses to the frontal lobe, would interfere also with good frontal lobe function and lead to confusion.

*Conception of Epilepsy's Pathologic Physiology.*—My conception of the pathologic physiology of epilepsy includes a state of disturbed frontal lobe function, a mental confusion, as the immediate precursor of the individual attack. The confusion is based upon an inadequate capacity of the frontal lobes to handle a bombardment of cerebral neurons by unusual volleys of afferent stimuli.

*Substantiated by Electrophysiologic Experiments.*—My conception is substantiated by facts derived from recent study and experimentation on the electrical activity of the brain. Confused mental states, associated with imperfect (disturbed) frontal lobe function, produce abnormal fluctuations in electric potential marked by a rhythm of amplitude and frequency approximating in character that occurring during an epileptic attack. Lennox, Gibbs and Gibbs<sup>8</sup> find that the typical disturbance in electrical potential led off from the surface of the skull during petit mal (the outburst of waves of great amplitude and reduced frequency) comes chiefly from the frontal lobes. With such limited capacity for good frontal lobe function as occurs in early infancy, mental deficiency, during sleep in the normal, and other conditions characterized by disturbance of consciousness or extreme mental confusion, such as result from breathing pure nitrogen, overventilating the lungs with room air, and failure of the cerebral blood supply, the amplitude of the waves in the cortical electrogram, is greatly increased, and the frequency is slowed (Gibbs, Davis and Lennox<sup>9</sup>). Davis and Davis<sup>10</sup> showed that babies under six months give large random waves rather than regular rhythms. Regular rhythms of about 4 waves a second begin to appear at about six months. The frequency increases progressively to 7 or 8 waves a second in childhood, and to the adult pattern and frequency by ten or twelve years. Kreezer<sup>11</sup> found that in low-grade mental deficiency large waves of longer duration, and frequency of about 5 waves per second, occurred.

*Intracerebral Occurrences During Epileptic Attack.*—*Fright as an Excitant.*—Gowers stated many years ago that as a direct incitant of the first attack, intense sudden alarm takes the first place. It can be traced in a considerable proportion of cases. In many instances the cause of the alarm seems absurdly inadequate, but that which seems inadequate on first sight may not seem so on further consideration. Gowers also said that the disturbing effect of sudden fear seems the greater when it cannot have its normal consequence, namely, the energetic discharge of the motor centers, to escape from danger.

The chief centers for the control of emotional reactions are located in the diencephalon. Strong emotional excitement invariably results in an immediate discharge of nervous impulses

through the autonomic nervous system. The immediate reactions invoked tend in general to produce functional responses which are beneficial to the individual. For example, there may be a charge of adrenin into the blood stream with consequent changes in the blood flow, or blood sugar may be mobilized for the possibilities of extreme muscular exertion. There may be a marked rise in the number of red blood cells in the blood.

Gibbs, Davis and Lennox tell of two of their patients with grand mal seizures who could be thrown into a seizure by a loud noise. The noise was followed within one-tenth second by a seizure. I have known numerous instances of anxiety and fright being incitants of attacks. J. S., a boy of eleven, whose first attacks were attributed by the family to a period of anxiety and excitement following his being involved with some other children in a petty theft from a local candy store, is one of them. Sudden fright had repeatedly caused later attacks. One afternoon, hearing a knock at the door and expecting his mother, he ran to the door and threw it open. Instead of his mother, he was surprised to find two Catholic nuns. Something in the surprise and in the strange picture of the hooded sisters gave him an excessive fright. He went down almost immediately in a generalized convulsion. It is probable that repetition of frightening situations in dreams may act in the same way. It is probable also that disordered visceral function, hunger, pain, nutritional lack of various kinds, may bombard the cerebrum with excessive afferent stimuli all below conscious levels and act as inciting factors of single attacks. But if we take one generally agreed on, like fright, and trace its probable intracerebral occurrences, a comprehensive view of the biodynamics of epilepsy may be gained.

*Intracerebral Occurrences Following Fright.*—What J. S. saw was carried from his retinae over the optic nerves and tracts to the geniculate bodies and to the occipital cortex. An attempt to associate it with things previously seen, heard and experienced, stored throughout his brain as memories, so as to adjust himself to appropriate present decision or action, a frontal lobe function, apparently failed. A condition of panic and fear evoked primitive defense mechanisms in the diencephalon. Stimulation of the autonomic nervous system followed, and poured into the blood stream the substances sympathin and

acetylcholine, humoral excitants of sympathetic and parasympathetic functions, to prepare him for flight or fight. It is known that each of the billions of red blood cells in the body contains a charge of electricity. The blood cells of a full-grown man have been estimated to contain sufficient electricity to light a 25-watt bulb for five minutes (Biol. Lab., Cold Springs Harbor, L. I.). Autonomic excitation, therefore, increases the electrical charge of the blood stream when it stimulates an immediate production of blood cells. This bodily turmoil bombards the brain, indirectly the frontal lobes, with extra volleys of afferent stimuli. These stimuli mean an increase in the volume of electrical potential being transferred over conduction neurons, a heavier load of electric current which overtaxes the impulse handling or current carrying capacity of fibers. How these volleys of electrical stimuli arrive in force and time to evoke fits must be left for lengthier and more technical descriptions which comprehend the interesting phenomena now being uncovered by the research electrophysiologists relating to the various alterations in spike potential, negative after-potential, and positive after-potential.

**Treatment.**—*Hospitalization.*—The treatment of a patient with convulsions is an individual problem, and if a period of preliminary hospital observation is possible, it is to be recommended. This provides an advantageous opportunity not only to determine the character of the fits but to make an appraisal of much concerning the patient which will help in his future management. A detailed description of the past and present condition is essential and can be obtained at this time. A study of his physiologic functions and a search for organic abnormalities and infectious or other disease processes is only slightly more important than the discovery and correction of bad hygiene in such matters as sleeping, eating and elimination. The more learned regarding the patient's mentality, aptitudes, interests, moods, and also relatives and friends, the more comprehensive the advice which can be given on many points important to favorable progress. It will be possible usually to classify as to primary or secondary defect epilepsy and to diagnose for proper treatment such secondary causes as lues, brain tumor, degenerative diseases and traumatic lesions. The endocrine status can be estimated better with the various diag-

nostic and laboratory aids available in a hospital, and the individual response to various useful medications, the personal preferences or peculiar sensitivity to various foods and any allergic reactions witnessed and recorded.

*Periodic Visits.*—Following the period of hospitalization, regular and frequent observation should be continued over a long period and records and charts of fits and therapeutic measures accurately kept, for in this disorder success in treatment so frequently lies in infinite patience and a persistent attention to detail. The advisability of checking, modifying, and perfecting at regular intervals the important points in daily hygiene and medication cannot be overemphasized. On these routine visits it is well to obtain information regarding all important bodily functions and to reexamine the muscular power, the reflexes, and the cranial nerves, especially the optic disks. A constant vigilance in this regard may disclose, even after long years, a hitherto quiescent brain tumor. So important are the routine visits over a long time that to a certain class of patients, likely to be negligent in making these visits, it may be well to administer a hypodermic injection of iron or some useful remedy, the necessity for which may be comprehended more readily than periodic examination and check-up of therapy.

*General Considerations.*—The range of mentality in epilepsy is from the superior, even gifted, to idiocy. With the lower grades of mentality successful treatment outside an institution is difficult. The best results are with patients having ability and willingness to cooperate. Schooling, occupation, and normal social life are as important for these patients as for any other person and should be strived for. The patient should not be permitted to regard himself as an abnormal person. Success in treatment is so possible in most cases that the epileptic is entitled from the start to a greater degree of optimism and hopefulness than unfortunately usually is vouchsafed him. Too frequently these points are neglected, and pessimism, inferiority and despondency arise which have to be treated in addition to the epileptic disturbance. Children are removed from school, deprived of normal companionship, ordinary pleasures and exercise, when such a simple measure as a small dose of phenobarbital at bedtime might be almost all that is necessary to control their tendency to fits.

Advice as to marriage and parenthood for these patients frequently is requested. There may be no reason why a patient whose attacks are under control should be denied marriage. Neither is there reason for parenthood to be denied, providing the tendency to fits was caused by a secondary defect of the nervous system, of toxic, inflammatory, or traumatic causation. No hereditary influence need be expected in such cases any more than a man who has lost a leg through injury need be expected to procreate a one-legged infant. Early statistics on the heredity of epilepsy were based chiefly on mentally defective institutional cases, mostly developmental defect epilepsy, and gave rise to a false picture of heritability. This is not warranted because the epileptic tendency from acquired defect causes is also prevalent among mentally competent and excellent citizens.

Besides the differentiation of primary defect and secondary defect epilepsy so that special treatment of secondary causes and defects responsible for the tendency can be instituted when possible, it is important to remember that the individual seizure is a disturbance in electrical conductivity among the cerebral neurons. Conditions and drugs which influence electric conductivity of cerebral neurons are of importance and have been studied. From the recordings of electro-encephalograms it is known that phenobarbital and sodium bromide prevent or alter the pathologic electrical activity associated with the seizure and these two drugs are the ones which for a long time have proved most successful in the treatment of epilepsy.

The bombardment of the cerebral neurons with excessive and unabsorbable afferent stimuli, which is in actuality an overloading with electric potential must not be forgotten, for it permits another influence to be exercised upon the disorder by treatment. These excessive stimuli may arise from disordered or diseased viscera, or from disturbed physiology due to improper care of the body. While sugar, oxygen, and lactic acid are said to be the only foods of the brain, improper nutrition of the body from a poorly balanced diet, inadequate mineral salts or vitamins, can be registered by electrical stimuli in the brain. Such a variety of disturbing afferent stimuli as may be set up by inadequate secretion of important endocrine glands, intrapsychic tension, mental conflict, fear and worry also must be taken into consideration.



The treatment of secondary defect epilepsy constitutes, in a word, consideration of two conditions, the tendency to fits and the causative factor. The appropriate treatment of the organic cerebral consequences of such secondary factors as tumor, lues, trauma, toxins, often may be quite obvious, but at other times will constitute an occasion for the use of experienced and conservative good judgment and the rarest skill. This statement applies particularly to various surgical measures for the alleviation of scar tissue, pachionian adhesions, and old traumatic lesions. We have witnessed a vogue for encephalography in epilepsy during the last few years. This painful procedure will frequently disclose air spaces over atrophic cerebral tissue, and enlarged ventricles. If the procedure be restricted to those cases in which a lesion, calling for operative interference, such as tumor, is suspected, and is not done routinely to expose situations for which surgical intervention is of no avail or contraindicated, it has its place. If the pathologic anatomy of epilepsy is appreciated properly, many abnormalities can be assumed without the patient being subjected to an encephalography, which in no way will alter the treatment of the case.

*The Average Case.*—For the average patient the amount of phenobarbital required may range from  $\frac{3}{4}$  to 3 grains daily. It is well to start with the smaller dose and increase it to the point necessary to control the seizures, when the patient has been put in the best possible environmental, physiologic, emotional and mental condition. A great many patients can be maintained free from attacks by comparatively simple treatment and routine supervision.

*The Difficult Case.*—The difficult cases are those with some situation or condition which cannot be adjusted easily, or whose cooperation is inadequate. Many of these difficult cases are burdened with numerous petit mal disturbances. Sometimes much larger doses of phenobarbital, gradually arrived at, or combinations of sodium bromide and phenobarbital will meet the problem. In others, mephobarbital, pentobarbital sodium and certain drugs acting upon the sympathetic and parasympathetic systems, as seem indicated by the condition of these systems, are of great assistance and may be used as accessories. Atropine, benzedrine sulfate, ergotamine tartrate, prostigmin, may be tried under close supervision.

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Regarding diet, much has been written, and certain ones extolled. My policy is to seek for a normal, well-balanced diet, suitable to the age, desirable weight and energy requirements of the patient. I especially wish to be assured of adequate protein. I find no benefit in inflicting the hardship of fluid deprivation, and make no restrictions of fluid intake except where there is evidence of inadequate output. In a word, the treatment of the epileptic is the humane consideration of the happiness, welfare, and general good health of a person whose brain is subject to occasional functional electrical disturbances requiring continuously, in some amount, some special medication such as phenobarbital or sodium bromide. *When* the patient is to be explored surgically is a matter for the judgment of a good neurologist convinced of the success of conservative medical treatment for almost all epileptic patients.

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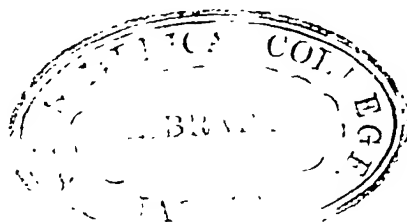


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pain is very severe and is associated with hematemesis or melena, should suggest the possibility of a penetrating type of lesion. Occasionally, a patient who has a duodenal ulcer will complain only of pain in the back, which has the usual characteristics of epigastric pain.

The pain in the thorax, which is most frequently diagnostic of a perforating peptic ulcer, originates in a well defined epigastric region, spreads from there upward along either margin of the sternum, and then extends into the depths of the thorax. This pain is usually lancinating and of short duration. At times, the pain seems to originate in a region buried deeply beneath the middle portion of the sternum. This type of pain occurs most frequently in the presence of perforating gastric lesions which are situated high in the stomach, but it may be present when only a duodenal ulcer is demonstrable at laparotomy. The pain in the thorax is almost always associated with pain in the epigastrium or with pain in the upper right abdominal quadrant, which comes on late following meals and has the characteristic sequence of the pain of ulcer. The severe epigastric pain which is referred to the thorax is not always relieved by the taking of food or alkali.

The pain caused by peptic ulcer usually occurs several hours after meals. If only a small amount of food is eaten, the pain usually comes on more quickly than it does after full meals.

Patients who have peptic ulcer often have distress which wakes them at night, but this is more noticeable among those who have duodenal or gastrojejunal ulcer than it is among those who have gastric ulcer. The manner in which pain of peptic ulcer is controlled is characteristic. Almost invariably, if the ulcer is uncomplicated, the pain will disappear promptly after the ingestion of food or of alkali, or often after the ingestion of even a glass of water. Change of posture, rest, sedatives, vomiting, or gastric lavage will also stop the pain promptly. The pain caused by penetrating ulcer or by acute indurated or obstructing ulcer is less consistently relieved by taking food or alkali.

Recently, we have been impressed by the beneficial effects on the pain and on the syndrome of ulcer in general, which follow the use of drugs which tend to cause relaxation. Large doses of belladonna, bromides, and barbiturates seem to control the pain of ulcer rapidly.

Nausea and vomiting are not uncommon in cases of duodenal ulcer. The nausea may arise while the pain is present or it may develop several hours after a meal and may be independent of pain. At times, the nausea is associated with regurgitation of small amounts of sour material. Taking some alkali, drinking milk, or eating a small amount of food may bring relief.

When vomiting ensues, as a rule, the nausea, as well as the eructation of acid material, stops, as does also the pain, which not infrequently accompanies these other symptoms. Vomiting frequently occurs at the time when the pain has reached its maximal intensity. The vomitus usually consists of a sour fluid which contains variable amounts of food. Occasionally, streaks of blood are noticeable.

A certain rhythmicity is maintained in the appearance and disappearance of the symptoms of acid eructation, flatulence, and vomiting. In some cases exactly similar experiences are repeated from day to day. Some patients perhaps become accustomed to the daily repetition of identical difficulties and, therefore, do not seek medical advice or treatment for a long time. When the syndrome loses this rhythmicity, it usually signifies that some complication is arising, that some obstruction to the normal gastric outlet is developing, or that deeper penetration of the wall of the viscus is beginning to take place.

*Gastrojejunal Ulcer.*—The general characteristics of the syndrome caused by gastrojejunal ulcer are similar to those caused by the original lesion. There is a tendency, however, for the symptoms of gastrojejunal ulcer to be more severe than those of the initial lesion. Periodicity is not so consistently a part of the syndrome as it is in cases of primary ulceration. The periods of relief are usually brief and often the relief is incomplete. Distress usually appears an appreciable length of time following a meal. It frequently comes on earlier, however, than it does in cases of duodenal ulcer. At times, pain occurs immediately following the ingestion of food, and then, after a few minutes, disappears, to reappear an hour or so later. Alkalies are more or less efficacious in the treatment of this type of ulcer. It is frequently noted, however, that the symptoms are not so promptly or so completely relieved in this way as were the symptoms of the original lesion.

The situation of the pain of gastrojejunal ulcer is usually characteristic. The patient will call attention to the fact that his pain is not in the region of the original pain, but is further to the left and lower than it used to be. The pain may originate in the region of preoperative pain and then may be referred downward. This is as characteristic as though the pain actually originated in the lower part of the abdomen.

The pain of jejunal ulcer, particularly if the ulcer is of the perforating type, frequently is referred to the back in a region definitely lower than the usual Boas' point, which is the characteristic site of the referred pain of primary ulcers. Nausea and flatulence, which occur at the time of the pain, are not unusual symptoms. These symptoms are frequently relieved by rest, or by the taking of food or an alkali.

Hemorrhage is not a rare complication of gastrojejunal ulcer. In 24 per cent of cases of gastrojejunal ulcer the history reveals that the patients have vomited blood or have passed tarry stools. The bleeding in these cases is usually intestinal and is more likely to be an oozing than a massive hemorrhage.

Careful questioning of patients who present themselves with a well established syndrome of gastrojejunal ulcer usually discloses the fact that prior to the development of definite symptoms there were periods of uncomfortable distention and complete absence of any desire to eat. Nausea is intense and the patient occasionally vomits large amounts of gastric residue. Unless such a patient happens to be seen during one of these brief attacks, nothing abnormal is demonstrable.

These periodic episodes of retention frequently antedate the recurrence of a consistent painful syndrome by many months. Spasm about the stoma, which is the result of early recurring ulcer or gastrojejunitis, is probably the cause of such episodes of temporary retention.

*Duodenal Stasis and Obstructing Lesions of the Upper Portion of the Small Intestine.*—It is generally assumed that it is extremely rare for pathologic processes to invade the upper portion of the jejunum or that portion of the duodenum distal to the site of an ulcer. There has developed, therefore, a false sense of security in assuming that the small intestine need not be seriously considered in most differential diagnostic considerations. The small intestine, almost in its entirety, remains



a relatively unexplored domain, and our knowledge regarding this portion of the intestinal tract seems lamentably inadequate. No doubt, thorough investigation of this region occasionally would furnish an explanation for some of the syndromes now catalogued under the diagnosis of "gastro-intestinal neurosis."

As an entity of clinical and pathologic significance, duodenal stasis has been discussed for many years. Unfortunately, certain physicians have been too ready to assume the presence of duodenal stasis on insufficient evidence as an explanation for many ill-defined syndromes, including distress in the epigastrium and in the upper right quadrant of the abdomen. Thus, there has arisen a healthy skepticism and some hesitancy in accepting duodenal stasis as an unquestionable explanation for conditions which produce prolonged or recurring dyspepsia.

Duodenal stasis usually occurs in consequence of an organic disease in which there is actual blocking of the intestine. Such obstruction may develop from intrinsic or extrinsic causes. The more important intrinsic causes are usually assumed to be congenital narrowing, foreign bodies, pressure by diverticula, benign or malignant tumors or inflammatory diseases of the intestinal wall. Potential extrinsic causes include bands of adhesions, either congenital or acquired, enlargement or ptosis of the right kidney, anomalies or diseases of the pancreas, or extension of inflammation of the gallbladder. Pressure by an aneurysm or pressure by lymph nodes surrounding the intestine occasionally causes duodenal obstruction. At times, prolapse of the duodenum or pressure behind it pushes the intestine against certain blood vessels, such as the superior mesenteric artery and vein, and causes intermittent or chronic interference with normal emptying.

*Duodenal Tumors.*—Benign tumors of the duodenum are extremely rare. Balfour and Henderson reported a series of six such cases. In five of these cases the patients complained of some indigestion. They complained of dull pain in the epigastrium or right upper quadrant of the abdomen and usually complained of some nausea and flatulence. In three instances these symptoms exhibited some characteristics suggesting peptic ulcer in that the distress reached its maximum several hours following meals and was relieved by food or alkali. Gastro-intestinal hemorrhages occurred in three of these cases. The

six tumors included two myomas, two adenomas, one adenomatous polyp, and one hemangioma.

Although carcinomas which originate outside of the duodenum not infrequently invade the organ, primary carcinoma of the duodenum is extremely rare. Encroachment on the lumen of the duodenum by malignant lesions originating in the pancreas or extrahepatic bile ducts may cause mechanical disturbances which produce nausea or vomiting. Rarely, the duodenum is completely blocked by such lesions.

**Reflex Dyspepsias.**—In this group we shall consider epigastric hernia and disease of the gallbladder, pancreas, appendix, jejunum, ileum, and large bowel. About a third of all patients who have symptoms of a gastric disturbance will have a disease included in this group. The reason for this is apparent when it is realized that embryologically and anatomically these organs are very closely related to the stomach. The stomach physiologically may be likened to the thalamus of the brain, in which coarse sensations are appreciated but not localized.

It is interesting to note that both chronic and acute diseases of these structures may make themselves known first by dyspeptic symptoms. In the acute diseases, however, there is usually a rapid progression of symptoms with signs of localization which clarify the diagnosis. Mild disorders or the incipient stage of a severe pathologic process may exist for months without producing other symptoms than those of dyspepsia. Regardless of a good history, thorough examination, and extensive laboratory tests, it may not be possible to make an early diagnosis.

**Cholecystic Disease.**—Disease of the gallbladder accounts for about 20 per cent of all dyspepsia, a percentage greater than that attributable to all organic disease of the stomach and duodenum combined.

In acute or subacute cholecystitis, the situation of the symptoms is usually well localized in the upper right quadrant of the abdomen. There is likely to be tenderness and rigidity in the right infracostal region. Tenderness increases as the palpating finger approaches the lower margin of the ribs. The gallbladder may be palpable. The distress is fairly constant and is not relieved by the ingestion of food; on the contrary,

alimentation usually intensifies the symptoms for a brief period. There may be much flatulence and there may be a qualitative relationship between the ingestion of food and the symptoms; fats and fried foods are especially likely to intensify symptoms. The syndrome lacks the precision and clock-like regularity of that usually seen in cases of uncomplicated peptic ulcer.

An icteric or subicteric tint to the skin is frequently noted and a slight elevation of the icterus index or value for the serum bilirubin further tends to localize the disease in the gallbladder or bile ducts. The vomiting of blood, even in small amounts, or the detection of blood in the stools, is almost certain evidence that the lesion is not in the gallbladder. Roentgenologic investigation may be the deciding factor in making the diagnosis.

The detection of gallstones in the cholecystogram will confirm the diagnosis. Stones which have become impacted in a duct usually produce symptoms sufficiently definite to permit an accurate diagnosis to be made. Even then, there is always the possibility of associated lesions.

The differentiation of chronic disease of the gallbladder with stones and uncomplicated peptic ulcer is usually not difficult. Blackford and Dwyer called attention to two clinical types of cholecystitis with stones: (1) attacks of gallstone colic for years and then the gradual onset of chronic dyspepsia, and (2) chronic dyspepsia with milder attacks of acute indigestion, often followed by biliary colic. A carefully taken history almost invariably will disclose evidence which will suggest the presence of gallstones. The severity of gallstone colic is not easily forgotten and patients as a rule call attention to acute indigestion which they experienced perhaps many years previously.

The pain of gallstone colic usually comes on without much warning and it frequently stops just as quickly; however, it leaves residual tenderness in the upper right quadrant of the abdomen. Often, the site of the pain is epigastric, although it may start in the upper right quadrant of the abdomen. Usually, it is a deep-seated, through-and-through pain which often extends to the neck and right shoulder. It is severe, may be lancinating, and is often described as a pain "from which there seems to be no escaping except by hypodermics or vomiting."

The pain is intensified by associated upper abdominal flatulence which is severe. The breathing seems to be cut off because a deep breath intensifies the symptoms. Emesis occurs at times and the vomitus is usually greenish or yellowish. The attack may terminate quickly, with or without vomiting, but occasionally several hypodermic injections or even an anesthetic may be necessary to control the pain.

The cholecystogram has been of unquestionable value in helping to detect certain instances of cholecystic disease in which the symptoms were very indefinite and in which a pre-operative diagnosis otherwise would have been impossible. The so-called "reflex" of the gallbladder as a cause of indigestion is extremely indefinite. Clinical syndromes that have been assumed to be diagnostic of chronic disease of the gallbladder have been presented from time to time. These syndromes may include indefinite epigastric discomfort following meals, much flatulence in the upper part of the abdomen, nausea or vomiting after meals, and belching and bloating after the ingestion of certain types of food such as fats, fried foods, onions, or apples. In our experience such syndromes are unreliable as indications of cholecystic disease. We have noted that best results following surgical treatment of cholecystic disease in cases in which there was definite clinical evidence of the disease. This was also the observation of Judd, who carefully analyzed the surgical results in various types of cholecystic disease. He found encouraging results in cases in which there were inflammatory changes in the wall of the gallbladder even though these changes were slight; however, if the patient's symptoms are of the chronic dyspeptic type the likelihood that cholecystectomy will effect a cure is not so great.

*Appendicitis.*—Appendiceal dyspepsia may be classified as acute, subacute and chronic. In the acute and subacute forms the onset is usually characterized by epigastric discomfort or pain, fullness, belching, and nausea followed by vomiting which may or may not bring relief. The pain, which may originate anywhere in the abdomen, usually shifts to the middle or lower part of the abdomen and later becomes localized in the right lower quadrant. It must never be forgotten that the pain of acute appendicitis at times does not become localized over McBurney's point but may, as in the case of retrocecal appendi-

cititis, be found considerably above the usual site. Depending on the acuteness of the process there may be tenderness, muscular rigidity, fever and leukocytosis. The subacute form is difficult to diagnose because the symptoms are not acute and the signs not prominent. Accurate localization of the pain may not occur.

Some writers recognize a chronic form of appendicitis in which the symptoms are mainly dyspeptic in nature. There may be no history of previous acute attack of localized distress. It is our impression that periodic attacks of vague indigestion dependent on mild pathologic alterations in the appendix must be rare. Like the gallbladder, many normal appendices have been removed without curing the patient of his indigestion. An appendectomy or cholecystectomy may appear as a short cut to curing the patient, but the more logical course of action should be a laborious method of exclusion of other conditions or the watchful waiting for signs or symptoms which indicate localization of the process. Appendectomy for the cure of neurosis is usually a disappointing therapeutic procedure.

*Pancreatic Disease.*—Gastro-intestinal symptoms dependent on disease of the pancreas are common. In a review of eighty-eight cases of pancreatic neoplasms in which jaundice did not occur, Eusterman and Wilbur found that the most prominent symptoms were gastro-intestinal dysfunction, pain and loss of weight. The pain may simulate the pain of peptic ulcer, but it usually is more severe and persistent. The distress frequently originates in the umbilical region but it is situated often to the left of the umbilicus and is referred to the back; at times it is of such a severity as to require opiates. The character and situation of the pain, and the loss of weight, particularly if associated with putty-like, loose stools, should suggest pancreatic disease. In addition, if jaundice of even a mild degree becomes apparent or if a palpable mass is felt, suspicion should be directed to the pancreas. We recently saw a middle-aged man who had been ill for only seven weeks. Following an attack of diarrhea, which had lasted a few days, he had noticed a progressive anorexia, epigastric fullness, loss of weight, and steady, unremitting pain which was situated in the lower part of the thorax and extended bilaterally around the lower ribs. When he was admitted to the hospital there was a subicteric